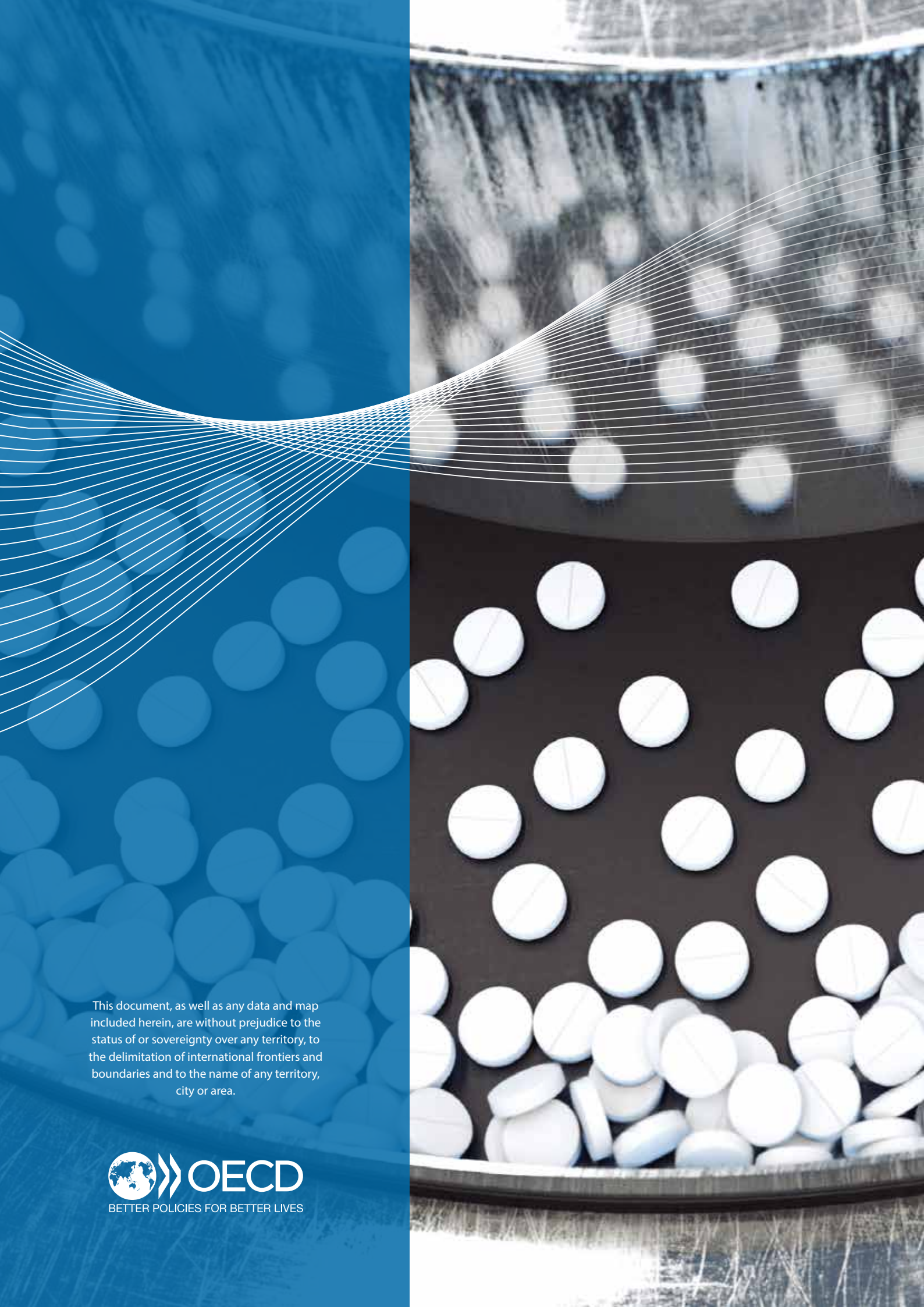




Enhancing economic performance
and well-being in Chile

Policy Actions for affordable and accessible pharmaceuticals





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ACKNOWLEDGEMENTS

This report is the result of the work of an OECD interdisciplinary team bringing together the Economics Department (ECO), the Employment, Labour and Social Affairs Directorate (ELS), and the Financial and Enterprise Affairs Directorate (DAF), with the support of the *Oficina Productividad y Emprendimiento Nacional* (OPEN) of the Ministry of Economy, Development and Tourism of Chile.

The work was led by Filippo Cavassini and co-ordinated by Fatima Talidi (ECO). The report was prepared by Fatima Talidi, Andres Irrazaval, Francesca Papa, Filippo Cavassini (ECO); Cristian Herrera, Valerie Paris, Ruth Lopert, Suzannah Chapman (ELS); and Pedro Caro de Sousa (DAF). The authors also gratefully acknowledge the contributions of Daniela Moya Holz, health expert. Alvaro Pereira, Director, and Isabell Koske, Deputy Director, Country Studies (ECO); Francesca Colombo, Head, and Federico Guanais, Deputy Head, Health Division (ELS); and Antonio Capobianco, Head, Competition Division (DAF) provided guidance and inputs to the report. Andrew Esson prepared the report for publication.

The preparation of the report was supported by the Ministry of Economy, Development and Tourism's *Oficina Productividad y Emprendimiento Nacional* (OPEN) led by Camila Carrasco, with the support of Teresita González, formerly Cabinet Advisor at OPEN. The report also benefited from inputs and insights from numerous Chilean institutions and stakeholders. Special thanks go to Lucas Palacios, Minister of Economy, Development, and Tourism of Chile, and to José Ramón Valente, and Juan Andrés Fontaine Talavera, former ministers of Economy; María Paz Grandon, Director of the Public Policy Division (Dipol), Ministry of Health; Heriberto Garcia, Director, and Patricia Carmona Director of Registers, National Health Institute (ISP); Carlos Bravo, Chief of Agencia Nacional de Medicamentos (ANAMED); Gastón Fernandez, Head Regulatory Department General Directorate for International Economic Affairs, Ministry of Foreign Affairs; Sebastián Castro, Director of Market Studies, Fiscalía Nacional Económica (FNE); Gonzalo Jaque, Chief of Gabinete, and Omar Cáceres, Chief of the area of Seremi de Salud Región Metropolitana; Pedro Riveros, Assessor of the Seremi de Salud Región Metropolitana.

The OECD Team would also like to thank the institutions and stakeholders that shared information and insights in the course of a mission to Chile: Health Commission of the Chamber of Deputies, Colegio de Químicos Farmacéuticos, ProImed, Salcobrand, and Cámara de Innovación Farmacéutica (CIF).

1. Key findings and policy actions

MAIN FINDINGS	KEY ACTIONS TO BE CONSIDERED
Improving medicines registration processes	
<p>Time to marketing approval for new medicines tends to exceed established targets, and markedly increased in 2018.</p> <p>However, with the exception of 2018, approval times are not generally longer in Chile than in other regulatory agencies.</p> <p>Consistent with Chile's population size and GDP, the financial and human resources available for the evaluation of marketing approval applications are far less than those of the stringent National Regulatory Agencies (NRAs), yet the National Medicines Agency (ANAMED – <i>Agencia Nacional de Medicamentos</i>) is expected to manage similar numbers of applications.</p>	<ul style="list-style-type: none"> ● Continue revising the process for prioritising unmet medical needs and new products with high public health value for access to the abbreviated evaluation process. ● Continue updating priority lists for the marketing authorisation of generic medicines with therapeutic or bio-equivalence studies. ● Increase user fees to mobilise additional resources for the evaluation of marketing authorisation applications. With appropriate institutional changes, additional funds could be deployed to upskill and expand headcount of skilled staff, and to support skill development and capacity building. Transparency and conflict of interest rules should be further developed. ● Develop and strengthen international collaboration, including harmonisation of procedures through already established relationships with other regulators in the Latin American region, and expand to other agencies. ● Expedite the approval of applications for marketing authorisation by expanding mutual recognition and work-sharing mechanisms.
Ensuring bio-equivalence and interchangeability of generics	
<p>In Chile, some copies of originator products remain in the market without having submitted evidence of bio-equivalence to their reference products, and the requirement to demonstrate bio-equivalence is not yet imposed on all new entrants. This creates confusion among prescribers and patients, and compromises price competition.</p> <p>The word 'generic' is not defined in legislation/regulations and is commonly used in ways that are inconsistent with internationally agreed definitions.</p> <p>The Law on Pharmaceuticals 1 promoted prescribing by International Non-Proprietary Name (INN), but only suggested the inclusion of the INN for information purposes next to the brand name. The Law on Pharmaceuticals 1 introduced the concept of 'interchangeability' to promote substitution of originator products with bio-equivalent copies. However, the law does not allow pharmacists to substitute one generic with another.</p> <p>The word 'bio-equivalent' appears on the packaging of those generic products that have satisfactorily demonstrated bio-equivalence to the originator. Because this does not seem to be clear for consumers, branding remains an instrument for price differentiation even among generics. Generic uptake seems quite high by international standards and has been increasing since 2000, but most of it is in the form of branded generics, which are more expensive than unbranded ones. This undercuts the ability of generics to bring down the prices of medicines.</p>	<ul style="list-style-type: none"> ● Amend all relevant regulations to require all copies of originator products to demonstrate bio-equivalence, and ensure that: a) no further products are granted marketing approval without evidence of therapeutic equivalence, and b) no further extensions are permitted for submitting evidence of bio-equivalence by listed products. ● Amend regulations to harmonise terminology within Chilean legislation/regulations and with international standards to reduce confusion during implementation of policy reforms. All regulations should use and refer to the same terms; their definitions should be the same across regulations and norms. In particular, the terms 'generic' and 'interchangeable' should be clearly defined, and aligned with international standards. ● Amend regulations to promote prescribing by INN and to encourage substitution by pharmacists, including between generic products. Design evidence-based communication and educational campaigns for prescribers, pharmacists and the general public. ● Develop, update and publish a list of multisource products that are interchangeable, for the information of prescribers, pharmacists and the general public, and for integration into electronic prescribing systems. Test effective ways for emphasising generic drugs when structuring the e-prescribing platform.

2. Introduction and overview

Over the last few decades, Chile has achieved significant improvements in key health indicators: from increased life expectancy across the country to high growth in health expenditure and improved standards for the approval of generic medicines in line with international practice. Despite all these efforts, the public health challenges that Chile is facing would, however, strain any health system and there are still remaining challenges. In particular, this Assessment analyses important issues that Chile faces to ensure an efficient and well-functioning pharmaceutical sector, with a focus on two main areas: 1) Improving medicines registration processes; and 2) ensuring bio-equivalence and interchangeability of generics.

On the one hand, Chile's drug regulatory agency (ISP, Instituto de Salud Pública) has been classified as a level IV National Regulatory Agency (NRA), proficient and efficient in carrying out its regulatory functions of evaluating the efficacy, safety, and quality of medicines, and is considered a reference NRA by the Pan American Health Organization (PAHO) (Peña Ruz, 2010^[1]). However, like any NRA, ISP can encounter challenges in its functions. In particular, Chile faces demands from patients for faster access to novel medicines and from industry for rapid access to market. Therefore, an efficient and well-functioning marketing approval procedure is needed to ensure the timely availability of medicines in the market. This must be supported by an appropriate regulatory framework, human and technical capacity, and other resources to ensure the quality, safety, and efficacy of medicines entering the market. Limited capacity and resources can represent important challenges and may accentuate existing backlogs in medicine approval procedures. Ensuring that technical resources are deployed optimally is thus essential.

This Assessment analyses the key challenges for marketing authorisation of pharmaceutical products in Chile and assesses the performance of the Chilean regulatory agency in comparison with other agencies. It identifies a number of bottlenecks (such as prolonged approval times) and the respective policy strategies that Chile could implement. These include updates to priority lists and abbreviated procedures; enhanced capacity as well as strengthened regional and international collaboration.

On the other hand, Chile also faces important challenges for the market of generic drugs. For example, many producers are failing to comply with the bioequivalence criteria established in the recent Law on Pharmaceuticals 1 (2014) while confusion on the definition and quality of generics hinders higher uptake of generic drugs. The Assessment describes and analyses Chile's generics policies, in particular the current therapeutic equivalence requirements and the terminology used to describe multisource medicines. Examples of other countries' approaches to authorise pharmaceutical products and deal with generics are provided that may present options and actions for consideration in improving Chile's regulatory policies and processes. These include amending relevant regulation to harmonise terminology within Chilean legislation/regulations and with international standards, as well as adopting strategies to further promote prescribing by INN and developing, updating and publishing a list of multisource products that are interchangeable.

To support the achievement of these key policy goals, attention to the detail of public health policy implementation is key, as well as the engagement across the Chilean stakeholders and the society to make change happen at scale and at pace. To this end, the note includes a detailed action plan for the implementation of the suggested policy actions, with suggested timelines over the short and medium term, responsible authorities and milestones to track progress. These policy actions can be found in detail at the end of each chapter. Other policy options are briefly discussed as potential long-term considerations within each chapter. The actions proposed form a comprehensive policy package and are not intended to be alternative options, but rather, they constitute complementary measures to enhance Chile's pharmaceutical sector on various fronts and in specific areas of interest identified in collaboration with representatives of the Chilean ministries. Delays or failing to address some of the actions could weaken their impact.

The Assessment builds on information collected through a questionnaire responded by the Chilean government representatives, as well as meetings and interviews with key government institutions, private sector, research institutions and civil society conducted during an expert mission to Chile on 2-8 May 2019 and analyses of peer-reviewed and grey literature (such as reports of agencies and institutions).



3. Overview of the Chilean pharmaceutical market

3.1. THE HEALTH SYSTEM IN CHILE

Over the last decades, Chile has made great strides towards a well-functioning health system and public health architecture. This has enabled significant improvements in key health indicators and has allowed Chile to obtain a level of quality of life which approaches the OECD average with regard to the general health status of the population (OECD, 2018 [2]). For instance, the average life expectancy in Chile has risen faster than the OECD average over the past forty years, increasing by 17 years compared to 10 years. In 2015, it was 79.1 years – 76.5 years for men and 81.7 years for women. However, life expectancy is still below the OECD average of 80.6 years (77.9 for men and 83.1 for women) (OECD, 2019 [2]). Moreover, while most OECD countries had introduced universal health coverage by the 1970s and 1980s, Chile is yet to fully attain it. In Chile, access to healthcare coverage increased by 6.5 percent over the last decade, but the share of those with unmet health care needs is still high, at around 8% in 2015, compared with 2% on average across the OECD (OECD, 2017 [3]).

Health expenditure per capita grew by 5.9% in real terms from 2009 to 2016 – significantly above the OECD average of 1.4%. However, despite this effort, health expenditure per capita (1,977 USD PPP in 2016) remains less than half the OECD average (4,003 USD PPP), which is consistent with GDP levels. Health expenditure as a share of GDP in Chile (8.5%) is also below the OECD average (9%) (OECD, 2017 [3]). At the same time, household out-of-pocket payments¹ continue to finance a significant share of health care. In Chile, out-of-pocket expenditure is 50% higher than the OECD average – accounting for one-third (32%) of total health expenditure (OECD, 2017 [3]).

Health care financing in Chile is underpinned by a mandatory requirement to be insured, with employee contributions set at 7% of payroll income, linked to a guaranteed basic benefits package. Beyond the basic package, inequalities characterise the range and quality of health care services that Chileans can access. Health care is financed either by the state-funded National Health Fund – *Fondo Nacional de Salud*, most commonly known as FONASA – or by the private coverage schemes, the *Instituciones de Salud Previsional* (ISAPRE). FONASA covers around 78% of the population, 17-18% are covered by ISAPRE, and the remaining 3-4% by the Armed Forces insurance scheme (OECD, 2019 [2]).² Typically, high-income people are under ISAPRE, while the rest of the population is covered by FONASA (MINSAL, 2017 [4]). Despite some recent progress (e.g. ending price discrimination between women and men, and a reduction in price differences by age), ISAPREs compete in a poorly regulated market, selecting low risks and differentiating the premiums paid by enrollees (OECD, 2015 [5]).

1 Out-of-pocket payments are expenditures borne directly by a patient where neither compulsory nor voluntary insurance cover the full cost of the health good or service. They include cost-sharing and other expenditure paid directly by private households.

2 The numbers listed in a recent market study by the Fiscalía Nacional Económica are only marginally different. FONASA is said to cover 78% of Chile's population (14.2 million beneficiaries) (Fiscalía Nacional Económica, 2020, p. 43[7]).

In terms of access to medicines, people insured by the public insurer FONASA can receive medicines dispensed for free in public primary care and hospitals but have to pay the full price of medicines purchased in retail pharmacies. For people with private insurance (ISAPRES), medicines coverage depends on the insurance plan; it can be partial (i.e. with co-payment), total or null. Medicines covered by the 'Explicit Health Guarantees' scheme have to be covered and the level of payment is regulated.

Individuals' out-of-pocket spending for health care is amongst the highest in the OECD. Private insurers (ISAPRES) and the public system (FONASA) contract with different providers, effectively enforcing a public-private split in the provision of health services, with perceived quality markedly worse on the public side (OECD, 2015^[5]).

In addition to FONASA, the public institutions responsible for protecting population health, for designing and delivering policies to promote public health and improving the health status of Chileans include:

- The **Ministry of Health** sets health policies and supervises the functioning of the health system. The Ministry is organised in two Under-secretariats: i) the Under-secretariat of Public Health; and ii) The Under-secretariat of Healthcare Networks. The Under-secretariat of Public Health safeguards the right to health protection for all Chileans, by exercising regulatory functions to ensure access and quality, and sustained improvement of population health. The Under-secretariat of Healthcare Networks regulates and supervises the functioning of health networks that deliver health care service, such as hospitals and primary care services.
- At the regional level, the **Regional Health Authorities** in Chile (*Secretarías Regionales Ministeriales*, SEREMI) ensure compliance with national health norms, plans, programmes and policies established by the authority; protect populations from environmental risks; undertake and coordinate epidemiological surveillance and outbreak responses; and adapt health strategic plans to their respective regions, within the framework set by the national authorities.
- The **Institute of Public Health** (*Instituto de Salud Pública*, ISP) is responsible for laboratory controls, quality control and marketing authorisation of medicines, medical foods³ and other products subject to sanitary control. The ISP is also in charge of the authorisation and registration of medicines and other products; supervision of medical laboratories and monitoring and reporting to the Ministry of Health on the surveillance of antimicrobial resistance. Many of these functions are performed by the National Medicines Agency (ANAMED) within ISP.
- The **National Health Procurement Agency** (*Central Nacional de Abastecimiento*, CENABAST) ensures the availability of medicines and medical supplies to health care providers, including the majority of Chile's public pharmacies. All public procurement, including hospital equipment, is controlled by Chile Compra from the Ministry of Finance, the online system for procurement by public institutions.
- The **Superintendency of Health** (*Superintendencia de Salud*) supervises compliance of healthcare providers with accreditation standards, and manages the legal and financial obligations of social security institutions.

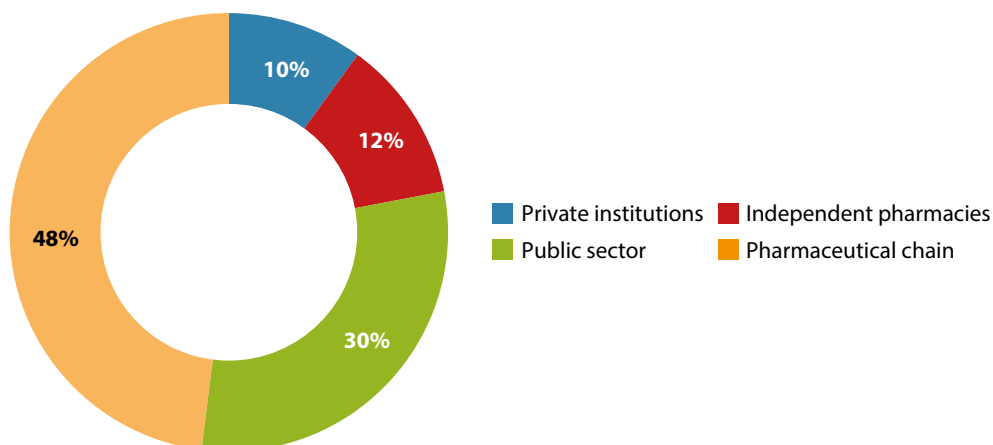
3.2. THE PHARMACEUTICAL MARKET

3.2.1. Structure of the market

Chileans can obtain medicines either through public health facilities or private pharmacies. Medicines purchased by CENABAST (*Central de Abastecimiento del Sistema Nacional de Servicios de Salud*) are made available to patients through public health facilities such as hospitals and primary care centres. There are more than 500 public health facilities where Chileans can obtain medicines across the country. Medicines are supplied free of charge (with a prescription) for Chileans who are covered by FONASA. In addition, Law N°21,198 empowers CENABAST to carry out the intermediation of health products through an agreement with pharmaceutical stores, private pharmacies and non-profit health establishments. Through this agreement, a list of medicines to be brokered is drawn up and a limit is set on the marketing price of these medicines. The ISP is responsible for monitoring compliance with the maximum sale price in

³ Medical foods are foods that are specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone.

Figure 3.1 Composition of the Chilean market in percentage by value of medicines (2018)



Source: (Fiscalia Nacional Economica, 2020_[7])

pharmacies. This mechanism has been used by to the so-called “Popular Pharmacies” (public pharmacies, managed by municipalities) to offer cheaper medicines, albeit paid for out-of-pocket, than regular private pharmacies.

Chileans can also obtain medicines through private pharmacies, in which case they generally pay the full price out of pocket. In 2015, there were roughly 3,000 pharmacies operating across the country, i.e. 16 pharmacies per 100, 000 inhabitants.⁴ By comparison, the average density of retail pharmacies in the European Unions is 24.7 (OECD, 2019_[6]).

The distribution of pharmaceuticals in Chile is highly concentrated, which translates into generally high prices for consumers, as highlighted by in the 2020 report of the Chilean competition authority on the state of the pharmaceutical market (Fiscalia Nacional Economica, 2020). Three main wholesalers operate, with some levels of integration with manufacturers. At the retail level, there are three large retail pharmacy chains, each vertically integrated with one of the main wholesalers. The three main pharmaceuticals chains account for as much as 80% of the pharmaceutical retail market. There are also a number of independent pharmacies, which take up the remaining 20% (Fiscalia Nacional Economica, 2020, p. 21_[7]). Overall, the composition of the pharmaceutical market as of 2018 is such that: the retail pharmacy chains have 48% of the market by value, the public sector has 30%, private institutions have 10% and independent pharmacies have 12%, as represented in Figure 3.1. Pharmaceuticals sold outside the public sector are paid out of pocket by consumers.

In short, there are many different distribution mechanisms in Chile. At the same time, the impact of the market structure and of the existence of these distribution models on pharmaceutical prices needs to be assessed in the context of the specific market dynamics and regulatory framework in place in Chile. An implication of this complexity is that any intervention at a stage of the supply chain that does not take into account its impact on other levels of the supply chain is likely to have unintended consequences.

One of the retail chains is fully integrated – i.e. the wholesaler is integrated not only with the retail pharmacy chain, but also with manufacturers. Another of the main wholesalers sells not only to its retail pharmacy chain but also to independent pharmacies. However, it has been recently found that this vertical integration does not pose concerns, since the sale of vertically integrated medicines does not go above 9% for the retail chain that sells the most vertically integrated products (Fiscalia Nacional Economica, 2020, p. 22_[7]).

All pharmaceutical products available in the Chilean market must be previously authorised by the ISP on the basis of satisfactory documentation of efficacy, safety, and quality. Medicines in Chile are categorised slightly differently

4. Between 2015 and 2018, 3,809 pharmacies operated in the country (Fiscalia Nacional Economica, 2020, p. 21_[7]).

from most other OECD countries, where there are generally only two types of products (originators and generics). In Chile, there are originators (first version of a medicine developed and patented by a pharmaceutical company that has exclusive rights to marketing during the patent term and any period of regulatory market exclusivity extending beyond the expiry of the patent) and generics (pharmaceutical product that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product). However, the latter is divided into unbranded and branded generics (see section 5 for more details).

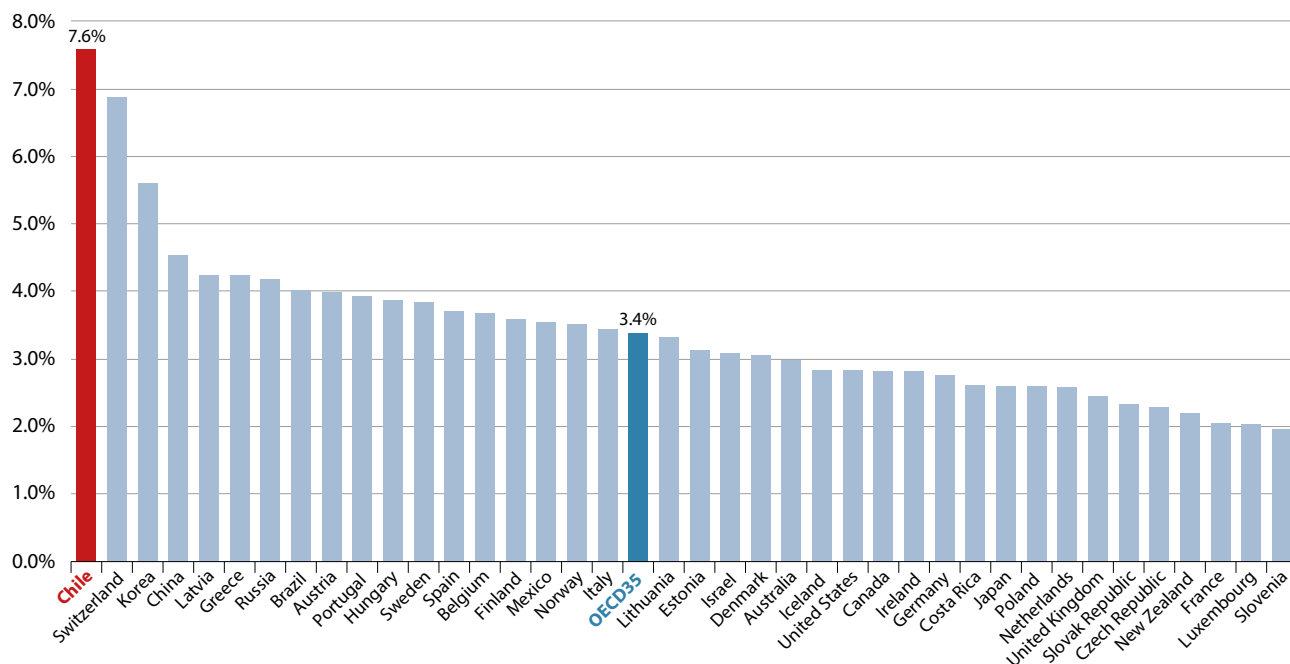
3.2.2. Consumption

With respect to consumption, the latest National Health Survey (Encuesta Nacional de Salud 2016-2017) showed that, when consulted, 65% of the population reported that they last obtained their medicine from the public sector, and 30% stated that they last bought it in a pharmacy (out-of-pocket). The survey also showed that almost 57% of the Chilean population takes at least one medicine per day, and this proportion has increased from 53% in 2010.

With medicine use on the rise, household out-of-pocket payments for health have become a significant part of the total budget of Chilean households. In Chile, out-of-pocket spending for health as a share of final household consumption is estimated as the highest among OECD countries and stands at 7.6% –more than twice the OECD average – see Figure 3.2. A significant share of these out-of-pocket expenditures comes from medicines bought at the retail market: expenditure on medicines makes up roughly 36% of Chilean households' out-of-pocket health spending on average (slightly higher than the 32% OECD average, see Figure 3.3 below). Medicines are consistently the largest component of health expenditure, with medical consultations next at 17% (Benítez, Hernando and Velasco, 2019^[8]).

Typically, more vulnerable households spend relatively more on medicines than the rest of the Chilean population. In particular, poorer and older households, as well as households composed mostly of women⁵ are disproportionately

Figure 3.2. Chilean out-of-pocket spending for health as share of final households' consumption, is the highest in the OECD (2017 or latest year)

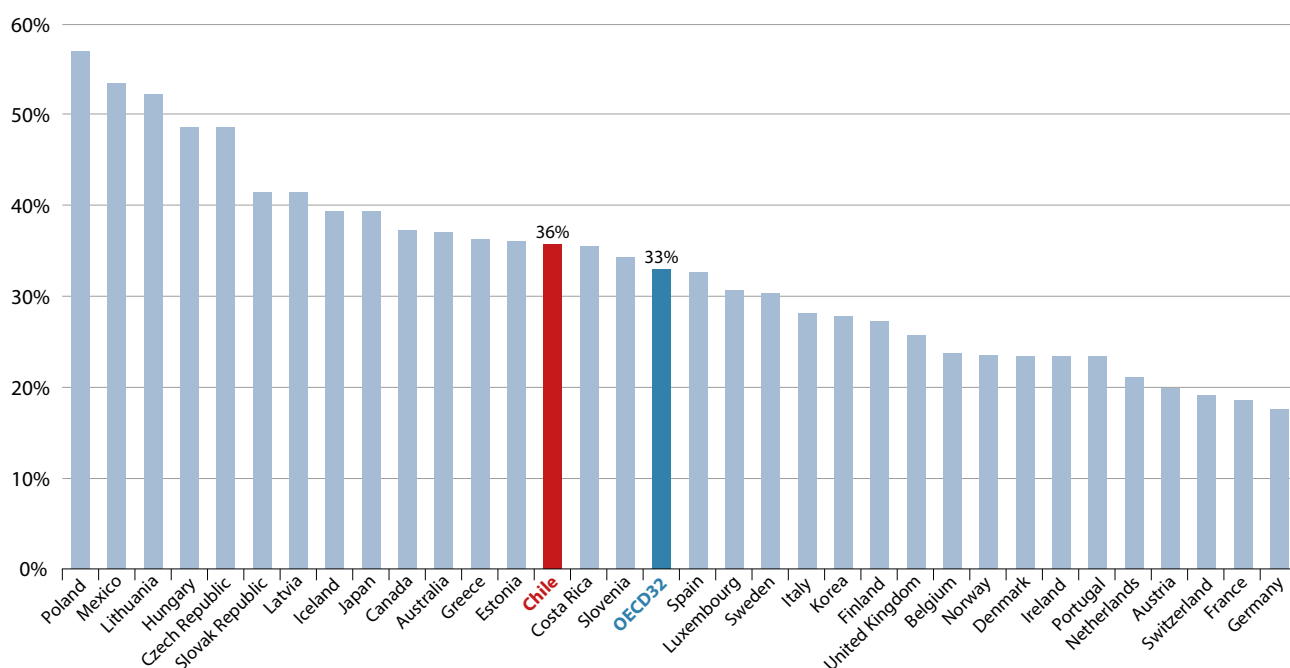


Source: OECD Health Statistics 2019, OECD National Accounts Database. For Chile: 8ª Encuesta de Presupuesto Familiar, Instituto Nacional de Estadísticas: https://www.inec.cl/docs/default-source/ingresos-y-gastos/epf/viii-epf/principales-resultados/informe-de-principales-resultados-viii-epf.pdf?sfvrsn=edcf54d2_8

5. This is not the case for those households who only have access to medicines through the public health system, since those households receives for free the medicines provided by CENABAST, hence they do not spend money on medicines nor supply themselves at the retail pharmaceutical market – However, CENABAST only supplies a limited number of medicines and for some specific health needs.

affected by the high out-of-pocket spending. For instance, for households buying medicines out-of-pocket, expenditure on medicines accounts for as much as 68% of the total health out-of-pocket expenditure by the bottom quintile, while, for the richest quintile of the population, expenditure on pharmaceuticals is 47% of their total health expenditure. With respect to older households, because they tend to use more medicines, they face on average higher drug expenditures, both in absolute terms and per capita, and they spend a significantly larger fraction of their total expenditure on drugs. On average, they spend 7.3 percentage points more on medicines (of their total health out-of-pocket expenditure) than younger households do, and they spend 37% more in value than households with fewer seniors. This occurs despite the fact that older adults receive a higher proportion of free medications than the rest of the population, with older people obtaining 63.6% of their medicines free of charge, compared to 42.4% for the rest of the population, according to the Encuesta Nacional de Salud 2016-17 by MINSAL. Similarly, FONASA users spent 8.5 percentage points more than ISAPRE users as share of total out-of-pocket health expenditure. Households with more women also devote relatively more money – although the difference is less striking (2 percentage points)⁶ (Benítez, Hernando and Velasco, 2019_[a]).

Figure 3.3. Pharmaceutical expenditure represents 36% of total out-of-pocket health expenditure by Chilean households (2017 or latest year)



Note: It is important to note that if we exclude the households that do not buy medicines out-of-pocket, the pharmaceutical expenditure as share of total out-of-pocket health expenditure in Chile would be 55%.

Source: OECD Health Statistics 2019. For Chile: CEP 2019 based on '8ª Encuesta de Presupuesto Familiar, Instituto Nacional de Estadísticas. https://www.cepchile.cl/cep/site/docs/20190130/20190130113629/pder502_abenitez_ahernando_cvelasco.pdf

6. Older households are households with at least 75% of senior members (more than 60 years-old), while younger households are those households with less than 50% of seniors. Households with more women corresponds to more than 75% female members versus households with 25% to 49% female members.



4. Improving medicines registration processes

4.1. STATE OF PLAY IN MARKETING AUTHORISATION OF MEDICINES IN CHILE

The Institute of Public Health (ISP) is responsible for granting marketing authorisation of medicines in Chile. All pharmaceutical manufacturers and companies selling pharmaceutical products must submit applications for marketing authorisation to the ISP in order to sell and distribute their medicines in Chile.

4.1.1. Authorisation procedures

Marketing authorisation procedures are outlined in DS¹ no. 3/10 (Ministry of Health, 2011). The marketing authorisation procedure consists of the systematic study and evaluation of the pharmaceutical, pharmacological, toxicological, and clinical properties of a product, with the objective of establishing its quality, safety, and efficacy (Ministry of Health, 2011_[9]).

Until the first half of 2019, applications for marketing authorisation were processed via one of three procedure types: ordinary, simplified and abbreviated.

The **ordinary procedure** is mainly used for new medicines (i.e. products containing a new active substance) seeking marketing authorisation (Ministry of Health, 2011_[9]). This requires the submission of a dossier containing evidence from pre-clinical and clinical trials to demonstrate the safety and efficacy of the new product (Figure 4.1). The marketing authorisation of products subject to ordinary procedure should be decided upon within a timeframe of 6 months (Ministry of Health, 2011_[9]).

On the other hand, the **simplified procedure** is generally used for extensions of indication, changes in formulation, generic medicines, and 'similar' medicines². Under DS no. 3/2010, copies of originator medicines assessed via the simplified procedure are not required to submit evidence from pre-clinical and clinical trials, nor original evidence of safety and efficacy unless the ISP determines otherwise. Marketing authorisation of products under simplified procedures should be granted in fewer than 180 days. For some active substances that have been 'listed' by the ISP, manufacturers are required to demonstrate therapeutic equivalence with the originator drug and must submit relevant bio-equivalence studies (Ministry of Health, 2011_[9]). For pharmaceutical products that are widely used and extensively trialled, applicants may present a literature-based submission to demonstrate safety and efficacy.

Finally, Article 51 of DS no 3/10 defines an **abbreviated procedure** (*proceso de registro abreviado*).³ This is similar to a *fast-track* mechanism — primarily for products to be used in Ministry of Health programmes. This procedure mirrors

1. Decretos Supremos are regulations.

2. 'Similar medicines' or *similares* are copies off-patent originator products that have been approved without demonstration of bio-equivalence.

3. The process is abbreviated in duration only.

both the ordinary and the simplified procedure (depending on the application), but with a shorter timeframe not exceeding 4 months (Ministry of Health, 2011^[9]). The abbreviated marketing authorisation procedure is intended for those products that have been included in:

- any programme of the Ministry of Health (MINSAL); or
- the national formulary (equivalent to an essential medicines list).

In addition to the existing abbreviated registration process (*proceso de registro abreviado*), the ISP has proposed an amendment to DS no. 3/2010 to further reduce the approval time for new medicines. In the current proposal, a new accelerated registration process (*proceso de registro acelerado*) would be introduced to further reduce the evaluation time for medicines fulfilling one (or more) of the following criteria: the medicine

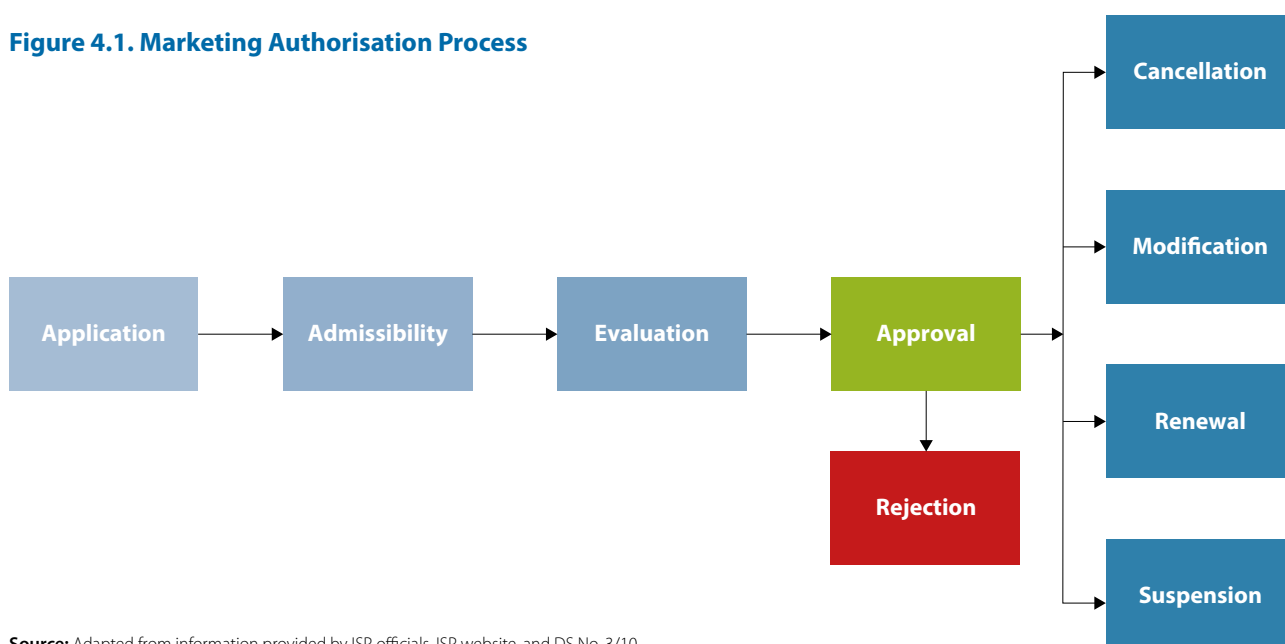
- is necessary according to the Ministry of Health (medicine has been included in MINSAL's health programmes/technical norms, and thus, is of public health interest);
- is necessary for the National Supply Centre (CENABAST) to supply the public health system of the country (also following MINSAL's programmes);
- is the first generic or biosimilar to enter the market; and,
- has already been approved by the FDA and EMA.

Decree No. 54 of November 7 2019 amended the decree No. 3 of 2010 of the Ministry of Health, approving regulations to generate an accelerated registration procedure for those medicines that already have a favourable health registration with another stringent Medicines Regulatory Agency.

The ISP has also requested to create a priority evaluation process that would accept data from early clinical trials (eg Phase I and II trials) for products considered likely to represent therapeutic innovations, on the basis of promising results in early stages of research for the treatment of serious or life-threatening conditions.

For all types of procedures, the ISP has its own format for applications, which can be submitted online through the system 'GICONA'.⁴ The overall stages of this procedure are described below and shown in **Figure 4.1**.

Figure 4.1. Marketing Authorisation Process



Source: Adapted from information provided by ISP officials, ISP website, and DS No. 3/10.

4. <http://www.ispch.cl/sistema-informatico-de-tramitacion-en-linea>

- **Admissibility** – prior to the submission of an application, the completeness of the dossier is assessed. This procedure takes a maximum of 10 days. If all requirements are addressed, an admissibility minute is issued within 5 days.
- **Submission of admissible application** – the application is officially submitted for evaluation.
- **Evaluation** – the submitted information regarding quality, safety and efficacy, legal, and administrative requirements are assessed separately. The evaluation stage has several parts:
 - Evaluators are assigned to assess quality, legal aspects, bio-equivalence (for simplified process for listed generic medicines), and process validation.
 - For new medicines – information on safety and efficacy gathered during clinical trials (Phase I to Phase III and preclinical studies) is assessed by the Pharmacology Society (external expert) or by an expert staff member. Pharmacokinetic studies are assessed by the Bio-pharmacy sub-department.
 - For ‘generic’ medicines that must demonstrate bioequivalence, the bioequivalence study is evaluated by the Bioequivalence and Therapeutic Equivalence Unit and the results are evaluated in the Process Validation Unit.
 - The quality of all medicines is assessed by the Quality & Pharmaceutical Equivalence Unit for non-biological products and by the Biological Products Unit for biological products.
 - The Legal Advice Unit of the ISP assesses compliance with the administrative, legal, and regulatory provisions that govern the marketing of pharmaceutical products as described in DTO 3/10, and which include registration or certification by the World Health Organization (WHO); authorisation of the production plant to manufacture medicines; Good Manufacturing Practice (GMP) certification.
 - Evaluators issue technical reports after assessment;
 - The Evaluation Commission assesses all these technical reports during an evaluation meeting. This is a committee that contributes to the evaluation of safety and efficacy information to provide approval or rejection recommendations. The committee comprises the chief of the department of National Medicines Agency (ANAMED), and members of the marketing authorisation sub-department, clinical trials department, new products department, pharmacovigilance, and the ANAMED’s scientific advisor, plus four external experts: pharmaceutical chemists or surgeons with academic, pharmacology or clinical background (Instituto de Salud Pública de Chile, 2012^[10]):
 - For new medicines, the committee, which includes external experts and a working group, meets once a month to assess the technical reports issued by the evaluators.
 - For other products, professionals from the Pharmaceutical Registry unit meet once a week to assess the technical reports issued by the evaluators.
 - After each meeting of the Evaluation Commission, a minute is issued. The minute is approved by the head of the Marketing Authorisation subdivision (*Jefatura de subdepartamento de Autorizaciones y Registro Sanitario*) and confirmed by the head of ANAMED where the decision is based on this minute and its recommendations.
 - If a product is rejected at the Evaluation Commission meeting, a resolution known as a ‘Probationary Term’ is issued, and further information is sought from the applicant within 6 weeks. If the applicant provides this information, the application can be re-considered; if the applicant does not respond or the information is unsatisfactory, the application is rejected.
- **Resolution and Registration** – following the evaluation, for cases in which the application is not rejected, the approval conditions are established, and the product is registered with a unique identification number.

4.1.2. Resources for evaluation of marketing authorisation applications

Within the ISP, the ANAMED (*Agencia Nacional de Medicamentos* – National Medicines Agency) is responsible for medicine assessments and marketing authorisation (See Annex B). The agency has seven staff departments: one administrative department and six technical-scientific departments. It employs 195 people. Currently, 45 staff members assess applications for marketing authorisation of medicines. The staff comprises:

- 14 evaluators responsible for assessing the safety, efficacy, technical, and administrative criteria (seven for new molecular entities and seven for generic medicines);
- 14 evaluators responsible for assessing quality, seven of whom work on biologic products and seven on non-biologic products (new molecular entities and generic medicines);
- 6 evaluators responsible for assessing bio-equivalence;
- 5 evaluators responsible for process validation;
- 6 staff members with legal backgrounds;;
- 6 external experts (members of the Assessment Commission⁵);
- External experts – medical practitioners and pharmaceutical chemists (*Sociedad de Farmacología de Chile*).

4.2. KEY CHALLENGES IN MARKETING AUTHORISATION IN CHILE

4.2.1. Approval times of marketing authorisations

According to the regulations, the marketing authorisation process should take a maximum of 180 days after the admissibility stage and the payment of the registration fee.

However, processing times often exceed this established target (Figure 4.2):

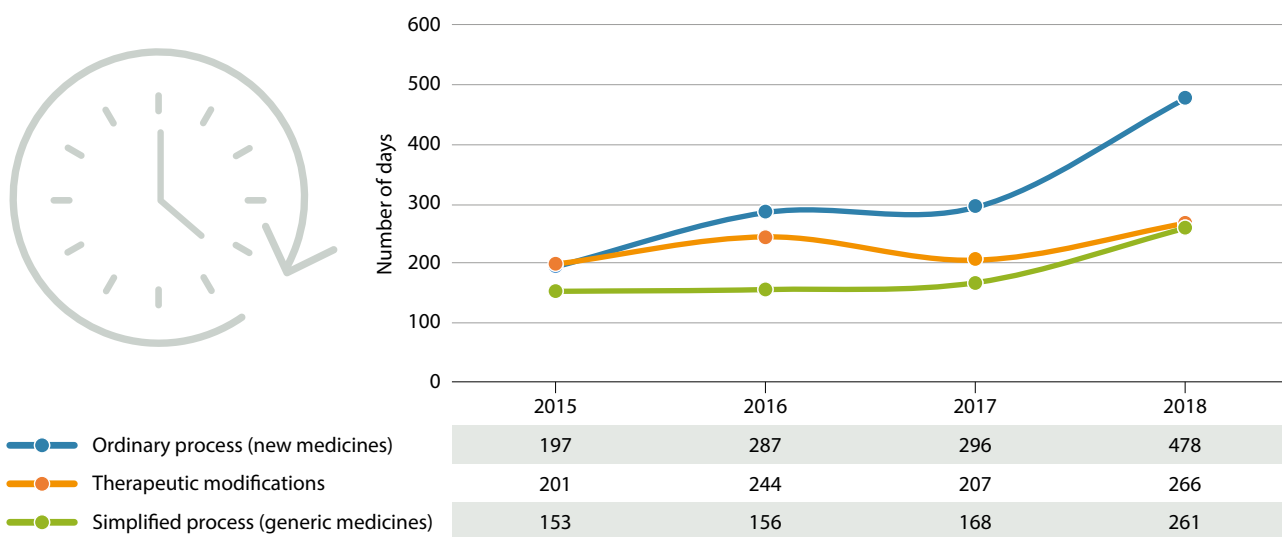
- The approval time for new molecular entities is between 6 and 18 months, and has increased in recent years. In 2015, the average time for marketing authorisation of a new medicine was 197 days; in 2016 and 2017, it increased to more than 280 days. In 2018, the average time was 478 days, well in excess of double the 180 days stated in the regulation. Since 2016, less than 20% of the ordinary processes for marketing authorisation have been concluded within 180 days (6 months). In 2018, only 3% of ordinary processes for new medicines were concluded within the 180 days established in the regulation.
- The approval time for the simplified procedures for the marketing authorisation of generic medicines (whether or not requiring bio-equivalence data) ranges from two to 12 months. The average processing time was 261 days in 2018, much longer than the average processing time of previous years, when it was less than 180 days (Figure 4.2). Nonetheless, from 2016 to 2018, more than 70% of simplified procedure applications have been resolved within the established timeframe (between 2 and 6 months).⁶

The number of applications submitted has not increased significantly over time, however there were fewer approvals in 2017 than in previous years and in 2018. It is worth noting that only one extra staff member was added between 2017 and 2018.

5. The Assessment Commission is made up of members of the Pharmacology Society who contribute to evaluation reports on clinical studies.

6. The result is that, taking together ordinary and simplified procedures, only 48% of applications between 2015 and 2018 are resolved within the timeframe set by legislation (*Fiscalía Nacional Económica*, 2020, p. 96₁₇).

Figure 4.2. Average processing times for marketing authorisation have progressively increased (2015-2018)

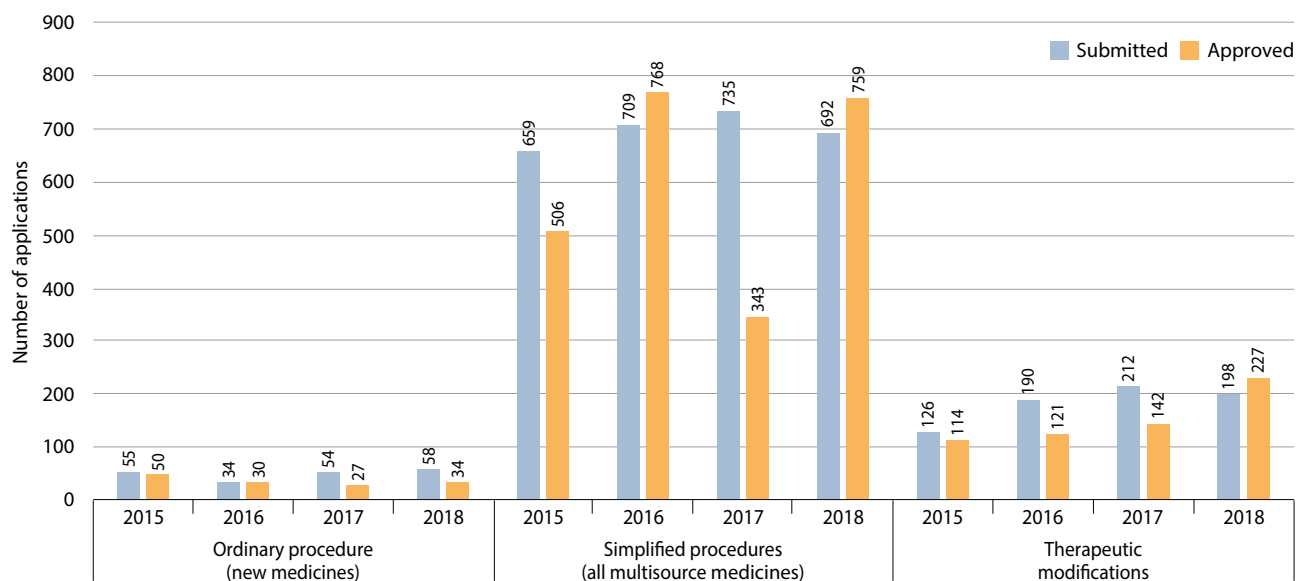


Source: Information provided by ISP officials.

Alongside longer processing times, the number of new medicines being approved as a proportion of the total number of applications has declined in recent years (reported by ISP). While 90% of applications received marketing authorisation in 2015 (50/55) and 2016 (30/34), just over 50% of applications received marketing authorisation in 2017 (27/54) and 2018 (34/58) (see Figure 4.3).

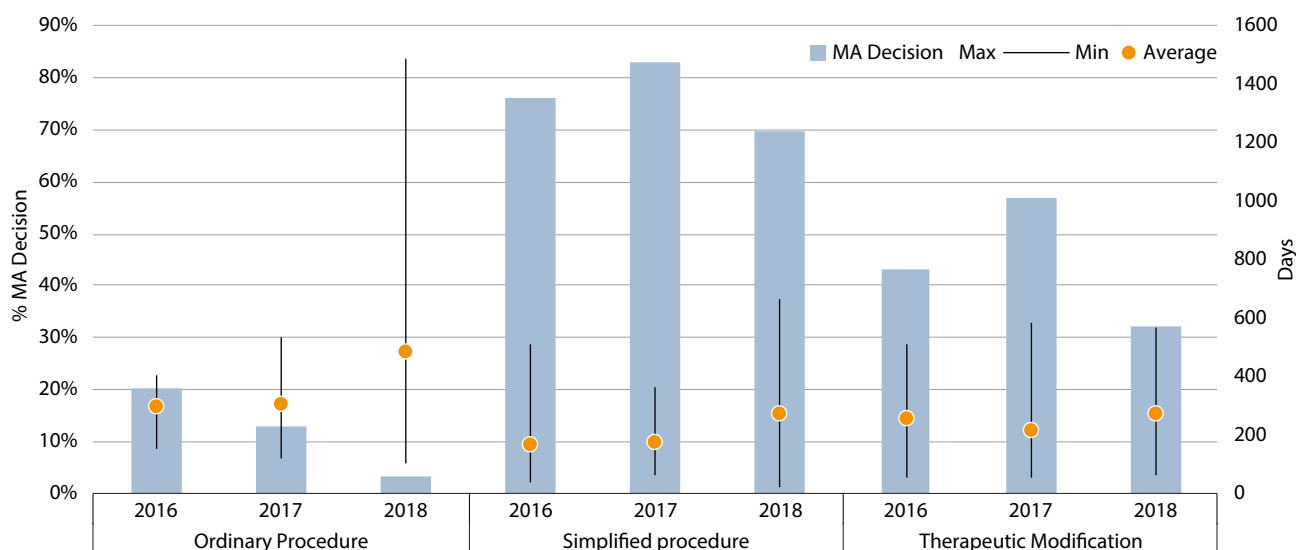
In parallel, the share of generic medicines being approved as a proportion of the total number of applications has varied since 2015. Between 2015 and 2017, between 40% and more than 70% of applications were approved annually. However, in 2016 and 2018, the number of approvals exceeded the number of applications, suggesting the existence of a backlog of applications from previous years. From 2015 to 2017, the number of applications for generic medicines increased from 659 to 735, but in 2018 the number of applications dropped to 692 (See Figure 4.3). In practice, approval times for generic medicines are between 2 and 12 months.

Figure 4.3. Overtime trends in marketing authorisation applications and approvals



Source: Information provided by ISP officials.

Figure 4.4. The proportion of decisions granted within the established timeframe has declined in 2018



Note: MA – marketing authorisation; Max – maximum; Min – minimum.
 MA Decision presents the percentage of marketing authorisation decisions within the established timeframe (180 days)
 Max – is the maximum amount of days reported to grant MA
 Min – is the minimum amount of days reported to grant MA
 Average – is the average amount of days reported to grant MA

Source: Information provided by ISP officials.

Furthermore, ISP has been receiving an increasing number of applications for therapeutic modifications. From 2015 to 2017, the number of applications increased from 126 to 212, and then dropped to 198 in 2018. Since 2015, there were more approvals than there were applications, suggesting the approval of residual applications from preceding years.

4.2.2. Comparing Chile’s regulatory performance to other countries

This section assesses the performance of the Chilean pharmaceutical regulatory agencies (notably ISP, ANAMED) by comparison with other selected National Regulatory Agencies (NRAs). Four agencies from OECD countries were selected for the comparison: COFEPRIS in Mexico, the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Therapeutic Goods Administration (TGA) in Australia. COFEPRIS was chosen because of the similarities between the Chilean and the Mexican pharmaceutical markets,⁷ and because both are considered regional reference authorities for medicines by PAHO (PAHO, 2018_[11]). The FDA, EMA and TGA were selected as they are considered stringent regulatory agencies.⁸

Scope of activities

The activities of the various NRAs differ widely in scope (see Table 4.1). The EMA only regulates human and veterinary medicines; TGA regulates medicines and medical devices, blood and tissues; other agencies have a broader scope of activities that includes the regulation of other products that can influence and affect health, such as food, chemicals, and tobacco. The FDA regulates medicines, food and beverages, products that emit radiation, and tobacco. In addition to medicines and cosmetics, the ISP and COFEPRIS regulate medical devices, blood and organs, food, beverages, water, chemical products (e.g. pesticides), tobacco, etc.

7. Chile and Mexico have comparable levels of pharmaceutical expenditures, both as a share of GDP (1.7% for Mexico and 0.9% for Chile) and per capita (259 USD for Mexico and 178 for Chile in 2011, last available year). The share of OOP spending allocated to medicines is higher the OECD average in both countries. Mexico used to have “similares” in off-patent markets in the past, and still have a very segmented off-patent markets with originators, branded generics and unbranded generics.

8. Stringent NRAs are internationally respected regulatory bodies or national regulatory agencies which are members or observers of the ICH or are associated with an ICH member through a mutual recognition agreement.

Human resources

Compared to the other NRAs, Chile's ISP has fewer staff involved in medicines evaluation (see Table 4.1). For example, COFEPRIS employs more than 100 evaluators, and its resources are augmented by external units that amount to more than 200 additional evaluators.

The FDA has more than 5,000 staff in the Centers for Drug & Biologics Evaluation and Research (CBER). The EMA has the capacity to mobilise its own staff, as well as staff of national regulatory authorities of EU Member countries and external experts, to conduct evaluations, amounting to thousands of evaluators (exact figure unknown). The Australian TGA has approximately 160 staff involved in pre-market activities for medicines, and makes extensive use of contracted external clinical evaluation resources for new prescription medicines.

Not surprisingly, the human resources available for evaluation are much more constrained in Chile than in the United States, the European Union, and even Australia. This is to be expected, given Chile's size and GDP, but since the number of medicines to evaluate and approve is not significantly lower than in other jurisdictions, maintaining rigorous standards and timely processes is a challenge for any NRA of this size. In the Mexican context, the number of staff available to evaluate medicines in COFEPRIS seems to be higher than in Chile, suggesting that, even taking into account income level, human resources could be increased.

Financial resources

The budget available to the ISP and ANAMED is also significantly lower than the budgets of other agencies, including COFEPRIS (see Table 4.1.). Moreover, user fees are low relative to those of the agencies selected for comparison, although not when compared with user fees in countries of similar income levels. Like COFEPRIS in Mexico, the ISP is mainly funded through a government budget allocation. User fees contribute only 6% of the agency's funding, whereas these account for approximately 45% of the FDA's budget, and 91% of EMA funding. The Australian TGA operates on a full cost recovery basis, levying fees for evaluation and annual charges for maintenance of registration.

This suggests that raising user fees or even seeking to approach full cost recovery, at least for those activities directly related to marketing authorisation of medicines, could be a useful source of revenue to increase the number and skills of human resources available for this activity. A change regarding raising user fees should be pursued in agreement with MINSAL and DIPRES, particularly, to increase accordingly the annual budget of ISP to conduct marketing authorisation activities.

Medicine assessment timelines and processes

While the selected countries differ with respect to the structure of their regulatory processes, all have a pre-submission stage, followed by the submission of an application that is then assessed to determine the quality, safety, and efficacy of the product, as well as any legal and administrative issues. If the application is satisfactory and approved, a registration number and marketing authorisation is provided and notified to the applicant.

The established processing time for marketing authorisation in Chile (180 days) is similar to Mexico (180 days), and the United States (180 days), and shorter than in the European Union (210 days) and Australia (255 days) (Table 4.2). Similarly to Chile, actual marketing authorisation processing times in the United States, the EU, and Australia often exceeded 180 days, while Mexico's actual approval times were shorter in 2017. Chile, the United States, and EU reported longer approval times than those stipulated in their respective regulations, while Australia and Mexico have been able to comply with theirs.

On average, actual processing times are higher in Chile than in comparator countries for new medicines. For copies of originators (with or without demonstration of bio-equivalence), they are higher than in Mexico, but lower than in other comparator countries. This suggests that the temporal issue is more acute for the evaluation of new medicines (see Table 4.3).

The long regulatory approval times of the EMA may be due to the complexity of providing marketing authorisation in all EU member states, which entails complex decision-making (Shah, Roberts and Shah, 2013). Moreover, the EMA has

Table 4.1 Information on regulatory agencies' resources - International Comparison

Country/NRA	Scope	Staff Numbers	Financing (000s USD)		Fees in 2018 (USD)	
			Financing Structure	Budget 2018	NM	Generic
Chile ISP	Medicines, human and animal, including biologics, psychotropics and narcotics; food for medical use; medical devices, tobacco, and cosmetics. Organ recipient registration. Control of laboratories (of chemical quality control, clinical, radiology, and other). Control of chemicals (e.g. pesticides). Quality of water and foods. Vigilance of antimicrobial resistance. Study of microbiologic agents causing diseases.	ANAMED: 37 evaluators 197 total staff members ISP: 841 staff members	Government's Budget (approx. 46%) + Registration Fees paid by industry (6%) + Other (e.g. transfers; Sale of Non-Financial Assets; Loan recovery - 48%) The budget allocated to pharmaceutical regulation accounts for 15% of the total budget	59,560	1,524	1,177
Mexico* COFEPRIS	Health establishments; medicines and other health supplies; disposition of organs, tissues, cells of human beings and their components; water, food and beverages, cosmetic products; cleaning products; tobacco, pesticides, plant nutrients, substances that are toxic or dangerous to health; biotechnological products, food supplements, raw materials and additives prevention and control of the harmful effects of environmental factors on human health, occupational health and basic sanitation.	141 evaluators 1651 total staff members Additionally: 165 evaluators from verifying units (TA)	The authorised revenues for each fiscal year are composed of the resources collected by fees, products, and uses plus the resources allocated by the government. It does not have an income budget or income of its own, what it gets is excess revenue from fees	40,615	7,400	4,139
United States FDA – CDER & CBER	Human and veterinary medicines, biological products, and medical devices. Food supply, cosmetics, and products that emit radiation. Tobacco products.	5750 staff in CDER 1174 staff in CBER 15100 total in FDA	Federal Budget authorisation (55%) + Industry User Fees (45%) Budget allocation to pharmaceutical regulation: Human drugs (30.2%) and Biologics (6.7% of total)	5,400,000	672,000	171,823
European Union EMA (and NRAs)	Medicines, for the benefit of public and animal health.	908 total staff in EMA Approx. 4000 evaluators in network	Fees and other income (91%) + General contribution (1%) + Orphan medicines contribution (4%) + Surplus from year N-2 (4%)	396,351 (EMA only)	344,510	103,424
Australia** TGA Medicines Regulation Division	Therapeutic goods: medicines, complementary medicines, medical devices, in vitro diagnostic devices, vaccines, blood products, and other biologics.	750 total staff; 160 staff in premarket activities for medicines, plus contracted external clinical evaluators	Fully cost recovered through fees and charges levied on sponsors and manufacturers of therapeutic goods	125,385	179,073	68,460

Note: CDER – Centre for Drug Evaluation and Research; CBER – Centre for Biologics Evaluation and Research; NRA – National Regulatory Agency; ISP – Instituto de Salud Pública (Institute of Public Health); COFEPRIS – Comisión Federal para la Protección contra Riesgos Sanitario (Federal Commission for Protection against Health Risks); FDA – Food & Drug Administration; EMA – European Medicines Agency; TA – Third Authorised Party (Tercer Autorizado); TGA – Therapeutic Goods Administration; MA Fees: Marketing Authorisation Fees – prices are in USD using the OECD average exchange rates in 2018.* Details of the financial structure and allocation of funds for pharmaceutical regulation in Mexico and Australia are not publicly available. **In Australia, the MA fees cover the application and evaluation.

Source: Based on each country's Applicable Regulations and reports (Kepplinger, 2015^[19]; Secretaría de Salud, n.d.^[119]; FDA, 2018^[135]; Sravani et al., 2017^[45]; Bujar, McAuslane and Liberti, 2016^[16]; Bujar, McAuslane and Liberti, 2018^[13]; COFEPRIS, 2018^[21]; COFEPRIS, 2016^[137]; Australian Government Department of Health, 2018^[138]; Australian Government Department of Health, 2019^[139]) (European Medicines Agency, 2018^[31])

Table 4.2 Information on marketing authorisations – International Comparison

Country	NRA	MA Validity	MA Approval Time per Regulation	Applicable Regulations
Chile	ISP	5 years	180 days	D.S. 3 Norma Técnica N° 131
Mexico	COFEPRIS	5 years	180 days	NOM-177-SSA1-2013 Regulation of Health Products (RIS)
United States	FDA	No limit but annual fees to keep the MA	180 days (generics & priority review) 300 days (standard review)	21 CFR 320 21 CFR 314 MAPP 5241.3
European Union	EMA	5 years	210 days (150 days accelerated assessment)	Directive 2001/83/EC Procedures for marketing authorisation Regulation (EC) No 1394/2007
Australia*	TGA	No limit but annual fees to keep the MA	255 days	Therapeutic Goods Act 1989 Therapeutic Goods Regulations 1990

Note: MA – Market Authorisation; NRA – National Regulatory Agency; ISP – Instituto de Salud Pública (Institute of Public Health); COFEPRIS – Comisión Federal para la Protección contra Riesgos Sanitarios (Federal Commission for Protection against Health Risks); FDA – Food & Drug Administration; EMA – European Medicines Agency; TGA – Therapeutic Goods Administration; PDUFA – Prescription Drug User Fee Act program
*Australian data are reported from July 2017-June 2018 in the 2017 columns.

Source: Based on each country’s Applicable Regulations and reports (Kepplinger, 2015; FDA, no date a; Sravani, Kusuma, *et al.*, 2017; Bujar, McAuslane and Liberti, 2016, 2018; COFEPRIS, 2017a, 2017b, 2018a; FDA, 2017, no date b; Australian Government Department of Health, 2018, 2019; European Medicines Agency, 2018b)

longer review periods during which additional information is sought and resolution of outstanding issues addressed (Hatswell *et al.*, 2016), though this activates a ‘stop clock’ provision and would therefore not be counted in the time to regulatory approval.

In addition, many applications for new medicines are submitted to the FDA and the EMA before being submitted in other countries (Downing *et al.*, 2012; Hatswell *et al.*, 2016). These agencies are often the first to evaluate new products, which may increase the likelihood of requests for additional information from companies. However, companies can take 3 to 6 months to answer, and during this time the clock stops and is restarted only when the information is provided (Shah, Roberts and Shah, 2013).

Although approval times are longer than in Chile and Mexico, NRAs of the United States, the EU, and Australia have all worked to reduce the variation in, and overall length of their evaluation timeframes, by pursuing greater consistency in their review processes (Bujar, McAuslane and Liberti, 2018_[13]). These countries have invested in improving the quality of applications by implementing measures such as pre-submission processes. They have implemented use of the common technical document (CTD) and subsequently introduced the electronic CTD (e-CTD) that has enabled expedited reviewing processes (ICH, 2018_[14]). These countries have also implemented priority systems for new and generic medicines to provide expedited marketing authorisation procedures (Van Hoof *et al.*, 2016_[15]; Bujar, McAuslane and Liberti, 2016_[16]; Liberti *et al.*, 2016_[17]; FDA, 2018_[18]). Priority systems were implemented by the EMA and TGA in recent years (2016 and 2017 respectively), while the FDA has progressively implemented priority systems since the late ‘90s (Kepplinger, 2015_[19]; Bujar, McAuslane and Liberti, 2018_[13]). Previous research suggests that the approval times at the FDA and the EMA are similar for those products that have undergone fast-track procedures (Shah, Roberts and Shah, 2013_[20]).

Mexico has also implemented strategies to expedite marketing authorisation, such as the establishment of a ‘New Molecules Committee’ to assess clinical data and other relevant information about new medicines entering the Mexican market. Furthermore, the regulatory assessment activities undertaken by COFEPRIS are supported by ‘Authorised Third parties’⁹ (TAs) that work as ‘Verifying Units’, providing pre-assessment reports for marketing authorisation applications (COFEPRIS, 2018_[21]).

9. Mexico’s ‘Authorised Third Parties’ are entities/companies that have been certified by COFEPRIS to carry out and issue assessments and opinions on the fulfilment of regulatory requirements and/or to conduct studies for the purposes of health procedures or marketing authorisations (e.g. bio-equivalence studies). These companies report directly to COFEPRIS and comply with its regulations, but are contracted and financed by pharmaceutical companies to carry out dossier assessments, bio-equivalence studies, etc.

Table 4.3 Trends in marketing authorisations – International Comparison

Country	NRA	Year	Marketing Approvals			Time to Marketing Approval		
			New Medicines (n)	Generic Medicines (n)	Extension of Indication/Modification (n)	New Medicines (n)	Generic Medicines (n)	Extension of Indication/Modification (n)
Chile ⁽¹⁾	ISP	2015	50	506	114	179	136	201
		2016	30	768	121	274	156	244
		2017	27	343	142	298	168	207
		2018	34	759	227	433	261	266
Mexico ⁽²⁾	COFEPRIS	2015	537		NA	NA	NA	NA
		2016	515		NA	NA	NA	NA
		2017	407		NA	108	100	NA
		2018	375		NA	NA	NA	NA
United States ⁽³⁾	FDA	2015	45	580	NA	303	316 ⁽³⁾	NA
		2016	22	630	NA	333 ⁽³⁾	450 ⁽³⁾	NA
		2017	46	843	NA	243 ⁽³⁾	301 ⁽³⁾	NA
		2018	59	810	NA	244 ⁽³⁾	NA	NA
European Union ⁽⁴⁾	EMA	2015	39	34	54	266 (+ 131)	NA	NA
		2016	28	27	59	262 (+ 156)	NA	NA
		2017	30	30	51	234 (+ 146)	NA	NA
		2018	31	15	65	256 (+ 184)	NA	NA
Australia ⁽⁵⁾	TGA	2015	32	127	33	215	170	200
		2016	43	142	46	199	158	195
		2017	38	111	45	364 ⁽⁵⁾	172	202
		2018	41	104	53	363 ⁽⁵⁾	174	193

Note: MA – Marketing Authorisation; ISP – Instituto de Salud Pública (Institute of Public Health); COFEPRIS – Comisión Federal para la Protección contra Riesgos Sanitarios (Federal Commission for Protection against Health Risks); FDA – Food & Drug Administration; EMA – European Medicines Agency; TGA – Therapeutic Goods Administration; NA – information not available

- (1) Medicines approved per year for generic medicines for Chile includes all applications for copies of originator products through the simplified process requiring or not requiring bio-equivalence studies.
- (2) In Mexico, all medicines approved (generic and new medicines) are reported. From information available, it was not possible to distinguish between generic or new medicine for each product. Information on approval times is not publicly available, except for 2017
- (3) Approval times for the United States are reported as average approval times, since median values were not reported in the FDA's reports. Times are reported in "calendar days". For new medicines and biologics, reported time includes Information on product modifications or new use of medicines is not available
- (4) Information on the number of medicines approved only accounts for medicines approved by the EMA through the centralised procedure and does not account for other medicines approved through other procedures and by EU countries NRAs. For the EMA, average approval time is reported for centralised procedures and for new medicines only. The time taken by companies to respond to requests of supplementary information is indicated in parentheses. Information on average approval time for generic and extension of indications is not available.
- (5) Australian data are reported on: July 2014 – June 2015 for the year 2015, July 2015-June 2016 for the year 2016, July 2016-June 2017 for 2017, and July 2017-June 2018 for 2018. Reported processing time is the median time taken to grant marketing authorisation. Reports the number of days counting from the time of application to the time of approval and includes the time taken by companies to respond to requests. The statutory deadline of 255 working days applies to applications for marketing approval for both new and generic medicines, after which, if no decision has been made, the TGA forfeits 25% of the relevant evaluation fee.

Source: Based on each country's Applicable Regulations and reports (Kepplinger, 2015; COFEPRIS, 2017b; FDA, 2017; COFEPRIS, 2017a; Sravani, Kusuma, et al., 2017; Bujar, McAuslane and Liberti, 2016, 2018; COFEPRIS, 2018a; Australian Government Department of Health, 2018; TGA, 2018b; European Medicines Agency, 2018c, 2018b; Australian Government Department of Health, 2019; FDA, no date a, no date b; COFEPRIS, no date)

4.3. GOOD PRACTICES IN OECD COUNTRIES

All NRAs face demands from patients for faster access to novel medicines and from industry for rapid access to market. Limited capacity and resources represent challenges for any NRA, and may lead to backlogs.

Three key strategies adopted by countries to reduce backlogs and approval times are:

- **Ensuring that technical resources are deployed optimally** (see section 4.3.1.).
- **Implementing expedited regulatory pathways** for medicines targeting unmet medical needs (see section 4.3.2)
- **Harnessing international alignment and collaboration**, for example by relying or recognising assessments carried out by other recognised NRAs. (see section 4.3.3)

Ensuring adequate capacity

Adequate numbers of staff, with appropriate qualifications and levels of competence are critical to the proper functioning of a NRA. Indeed, a comparative 10-country study of drug regulation has even identified shortage of qualified staff as the main problem faced by regulatory authorities (Ratanawijitrasin and Wondemagegnehu, 2002_[22]). Countries have adopted different strategies to tackle capacity shortages. Some OECD countries, such as the Netherlands and Australia, are levying new fees on the pharmaceutical industry for each approval application, and using the resulting funds to cover increasing staff numbers and salaries (Matsebula, Goudge and Gilson, 2005_[23]). As an alternative strategy, many developing countries have recruited part-time drug evaluators (e.g. Medicines Control Council in South Africa, Health Professions Council in Zimbabwe, Drug Control Council in Tanzania).

In Chile, the ISP has fewer staff involved in medicines evaluation than other NRAs (see Table 4.1) and stakeholders (mission) reported that the 2017 backlog was the result of a surge in the number of staff members retiring. In addition, new technical units were established in the same year, necessitating staff training before becoming fully operational.

In forward planning, building on the experience of other countries, ISP must ensure that the available personnel (including external resources) are adequate for the projected scale of activity. While this seems obvious, it is particularly important as an increase in the number of applications can be expected in years to come, which will also bring the challenge of new technologies such as complex biologics and immunotherapies, among others. Staff separations (including retirements) should be anticipated where possible, and planning should include recruitment, training, and 'on the job' learning for new staff (Matsebula, Goudge and Gilson, 2005_[23]). The time and resources required to build future capacity must be factored into the activity plans of the ISP. Proper organisational structures and processes should be in place, which should define roles, responsibilities and activities of each staff member to ensure the proper functioning of the agency and the timely execution of regulatory procedures (Matsebula, Goudge and Gilson, 2005_[23]).

Furthermore, capacity-building activities should take into account the skills needed for the assessment of novel and emerging technologies. Specialised and highly qualified personnel, together with specific guidelines and regulations for these types of products, are required to ensure that ISP can apply appropriate assessment procedures.

4.3.1. Expedited regulatory pathways in selected OECD countries

In recent years, the United States and the EU have introduced facilitated regulatory pathways (FRPs), with a focus on reducing the processing times of medicines addressing unmet medical needs (Liberti, 2018_[24]; OECD, 2018_[25]).

To promote and accelerate the introduction of new medicines into the market, the FDA has introduced four expedited regulatory pathways: the Priority Review, Accelerated Approval, Fast Track designation, and Breakthrough Therapy designation (Kepplinger, 2015_[19]; Bujar, McAuslane and Liberti, 2018_[13]). All these mechanisms have in common that they are intended for medicines that address unmet needs in the treatment of serious or life-threatening conditions. Medicines can be designated in one or more FRPs (Center for Drug Evaluation and Research, 2017_[26]):

- *Priority Review* provides a reduction of four months in the projected review time by the FDA. To be eligible, a product must provide a significant improvement in safety or efficacy in the treatment, diagnosis, or prevention of a condition in comparison to available therapies. It is determined on a case-by-case basis, independently of whether the applicant company requested it.
- *Accelerated Approval* facilitates shorter clinical trials, by allowing a manufacturer to measure efficacy using a proxy outcome thought to predict the clinical outcome of interest. While drug approval typically requires clinical trials with endpoints that demonstrate a clinical benefit, such as increased survival for cancer patients, drugs with accelerated approval can initially demonstrate an effect on *surrogate endpoints* or intermediate clinical endpoints, such as reduction in tumour size. This enables the FDA to have more flexibility and reduce processing times by including endpoints that are “reasonably likely” to predict an important clinical benefit. The US FDA then requires companies to conduct further trials to confirm evidence of survival.
- *Fast Track Designation* can expedite the development and review of the product. Via a process known as ‘rolling review’, the FDA reviews “portions of an application” before the sponsor submits a complete application. Designation must be requested by the company. To be eligible, the product must demonstrate the potential to address an unmet medical need and address a serious condition (e.g. AIDS, Alzheimer’s, heart failure, cancer), either where no therapy exists or where the new therapy is potentially better than those currently available. Fast Track designation allows frequent interactions between the sponsor and the FDA review team. With this designation, medicines can be eligible for accelerated approval and priority review, if relevant criteria are met (FDA, 2018_[18]).
- *Breakthrough Therapy Designation* can expedite the development and review of an application by creating a collaboration and close process between the FDA and the sponsor through timely communication and efforts by the FDA to make the trials as efficient and limited as possible. To be eligible, the product must show preliminary clinical evidence indicating that the drug represents a substantial improvement in efficacy and safety over existing therapies on one or more clinically significant endpoints. It may also require additional data from *in vitro* studies or animal models. This designation may provide for rolling review, and the product may also be eligible for priority review (Kepplinger, 2015_[19]).

In 2017, expedited approvals took on average 240 days, while standard approvals lasted 365 days. In 2018, 41% of new medicine applications were designated as Fast Track; 24% were designated as Breakthrough Therapies. In 2018, 73% of new medicines approved underwent Priority Review¹⁰ and 7% were approved under the Accelerated Approval programme (Center for Drug Evaluation and Research, 2019_[27]).

The EMA also has in place an accelerated assessment process, which reduces the review timeframe of a marketing authorisation application by up to 150 days. An application may be eligible for accelerated assessment if the product is considered of major public health interest and a therapeutic innovation. Requests for accelerated assessment should be made two to three months before the application submission. Prior to the request, applicants should seek guidance from the EMA to ensure its timely submission (European Medicines Agency, 2018_[28]). In 2018, under the accelerated assessment process, procedures took an average of 230 days (197 days excluding company’s clock-stops) against 441 days for standard approval procedures (Bujar, McAuslane and Liberti, 2018_[13]; EMA, 2019_[29]).

Within the Accelerated Assessment mechanism, the EMA has also established the Priority Medicines (PRIME) scheme to expedite the evaluation and marketing authorisation of medicines considered priorities (Bujar, McAuslane and Liberti, 2018_[13]). PRIME promotes a dialogue between the EMA and the manufacturers to optimise development plans and expedite evaluation and approval processes (Van Hoof et al., 2016_[15]). PRIME is aimed at improving clinical trial designs to enhance the generation of data necessary for an application (European Medicines Agency, 2018_[30]). Under PRIME, medicine developers are assisted by an appointed rapporteur who provides continuous support and helps with

¹⁰ Note that some drugs underwent priority review as a result of a sponsor ‘voucher’ and may not provide significant therapeutic advance (Center for Drug Evaluation and Research, 2019_[27]).

the collection of evidence ahead of a marketing authorisation application. In addition, EMA provides guidance on the development plan and regulatory strategy, scientific advice, and confirmation of potential accelerated assessments (European Medicines Agency, 2018_[30]). Since its launch in 2016, the EMA has received 177 requests to be considered under PRIME; of these, only 36 medicines (21%) have been granted eligibility to PRIME (EMA, 2019_[29]; European Medicines Agency, 2018_[31]). Through this scheme, developers have made use of scientific advice and assistance by the EMA, which include input from multiple committees and stakeholders (e.g. HTA bodies and patient organisations) (EMA, 2019_[29]).

The adaptive pathways approach by the EMA seeks to enable new medicines addressing unmet medical needs to reach the market faster on the basis of fewer data (Davis et al., 2016_[32]). Adaptive pathways do not change the standards for the evaluation of the products or the marketing authorisations requirements. However, this approach is based on three principles: 1) the iterative development of medicines, where approval can be carried out in stages or by confirming the benefit-risk balance of a product after a conditional approval; 2) gathering evidence through real-life use to complement clinical trial data; and 3) involvement of health-technology-assessment bodies during the medicine's development (EMA, 2019_[33]). Under these adaptive pathways, medicines receive an initial marketing authorisation earlier in the development process on the basis of limited preliminary data. However, the EMA requires companies to provide and analyse 'real world data' (i.e. observational data) to supplement evidence from preliminary clinical studies and/or as an alternative to randomised clinical trials (Davis et al., 2016_[32]). Moreover, additional support is available through 'additional pre-submission meetings' prior to a scientific advice procedure meeting, which allows companies to discuss options before drafting clinical trial protocols that will be subject to scientific advice (EMA, 2019_[33]). This approach can support the development of medicines where gathering and generating data and evidence is challenging.

Other agencies have also implemented expedited pathways. For example, Japan's NRA has invested in speeding up the review of medicines by including additional resources, the introduction of pre-submission meetings to discuss clinical trial study results, and consultations approximately six months before submission of a new drug application (Bujar, McAuslane and Liberti, 2018_[13]). Brazil has taken action to strengthen the capacity of its NRA by establishing national and international technical cooperation agreements and a special registration procedure for imported generic medicines (Barra and De Albuquerque, 2011_[34]). Mexico has established priority lists to accelerate the resolution of applications, particularly for medicines of public health interest (Gonzalez Pier and Barraza Llórens, 2011_[35]). The selection criteria for prioritising medicines follow the health priorities of the country and characteristics of each product (e.g. utilisation, market share).

4.3.2. Strengthening the capacity of NRAs through international collaboration

The WHO has defined several types of international collaboration that can ease drug regulatory processes (World Health Organization, 2016_[36]; Kaddu et al., 2018_[37]):

- **Collaboration:** involves informal peer-to-peer information sharing between experts. It can be supported by the International Regulatory Cooperation agreements for information sharing between NRAs.
- **Regulatory Convergence:** a voluntary process whereby the regulatory requirements in different countries or regions become more similar or aligned over time. It consists in a gradual adoption of internationally recognised technical guideline documents, standards, and scientific principles, common practices and procedures, or the establishment of appropriate domestic regulatory mechanisms aligned with shared principles to achieve a common goal.
- **Regulatory Cooperation:** practices between NRAs aimed at efficiently regulating medical products. The range of formal mechanisms include the creation of joint institutions, treaties, and conventions. Less formal practices include sharing of information, scientific collaboration, common risk assessment, joint reviews, and developing standards. It may include working towards building regulatory capacity or providing technical assistance to contribute to the improvement of regulatory governance practices.

- **Regulatory Harmonisation:** the process by which technical guidelines are developed in order for participating authorities in multiple countries to adopt uniform practices. It seeks to expedite regulatory procedures, provide uniform guidelines, and shorten marketing authorisation times to speed market entry.
- **Reliance:** the act whereby the NRA in one jurisdiction may take into account and give significant weight to evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions it adopts, even when it relies on the decision and information of others.
- **Recognition:** the routine acceptance by the NRA in one jurisdiction of the regulatory decision of another NRA or other trusted institution. Recognition means that evidence of conformity with the regulatory requirements of a given country is sufficient to meet regulatory requirements of the country in question. Recognition may be unilateral or multilateral and can be subject to mutual recognition. It happens, for example, when countries accept approval decisions taken by other countries or international organisations, such as the International Conference on Harmonization (ICH).

In the European Union (EU), regulatory requirements have been extensively harmonised with different routes to marketing authorisation based on a single assessment system (Luigetti et al., 2016^[38]). One such route, the Centralised Procedure, allows applicants to file one marketing authorisation application that is assessed by a centralised committee allowing approved products to be marketed in all EU member states. Additionally, there are other registration pathways: the mutual recognition procedure (MRP) and the decentralised procedure (DCP). These procedures include filing the same dossier using identical specifications in all involved countries (Lakkis, 2010^[39]). This system enables any assessment report issued by one NRA of the EU network to be relied upon by any other. This has facilitated and expedited marketing authorisation of medicines in EU member states.

Other examples of harmonisation include the Gulf Cooperation Council (GCC) and the Association of South-East Asian Nations (ASEAN). The GCC was established in 1989 by Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen. The GCC has promoted the strengthening of the technical and administrative capacity of the individual regulatory authorities, and pursued the adoption of transparent and streamlined processes for marketing authorisation of pharmaceutical products in the region (Al-essa, 2011^[40]). In 1999, a pharmaceutical harmonisation initiative was launched by the Gulf Central Committee for Drug Registration (GCC-DR) to coordinate health policies and programmes among the participating members via exchange of information, knowledge, techniques, and expertise. The GCC-DR is responsible for the registration of pharmaceutical products, GMP inspection and compliance, approval of quality control laboratories, bio-equivalence studies, and review of technical and post-market surveillance (Lakkis, 2010^[39]). Following harmonisation of regulatory requirements, the GCC has in place a centralised registration procedure where the GCC-DR received the marketing authorisation application files; companies must submit file copies for each country. Each country assesses the application files and provides recommendation to the committee. The members states meet four to five times a year to discuss the review reports and the approval decision is made in agreement (Srivani et al., 2017^[41]). The committee then issues the approval for marketing authorisation and issues a single registration certificate. The centralised procedure is intended for generic medicines where bio-equivalence studies cannot be done (e.g. inhalers), biosimilar medicines, and medicines with narrow therapeutic spectrum, among others (Pateriya et al., 2011^[42]).

First established in 1967, ASEAN now comprises Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam. In 2000, ASEAN began efforts to harmonise the pharmaceutical sector, in an initiative led by the Pharmaceutical Working Group of the ASEAN Consultative Committee on Standards and Quality, which is made up of representatives of all the members' NRAs (Reggi, 2017^[43]). The initiative includes a public health and pharmaceutical harmonisation scheme that works to create harmonised guidelines for the regulation of pharmaceuticals, a unified set of technical requirements, and a standard format for drug registration applications (ASEAN CTD). The harmonisation initiative also includes a mutual recognition agreement (MRA) on bioavailability and bio-equivalence data through data sharing, and the establishment of a common list of reference products for

generics (Lakkis, 2010^[39]; Reggi, 2017^[43]). The ASEAN NRAs have begun joint assessments of applications simultaneously submitted to all participating NRAs; decisions on the applications are made by each NRA based on this joint assessment (Reggi, 2017^[43]). These joint assessments have fostered discussions leading to the improvement of procedures and collaboration between NRAs, as well as technical and knowledge transfer leading to mutual trust (Reggi, 2017^[43]).

Other countries have implemented reliance and recognition mechanisms to augment the capacity of their NRAs. Countries such as Canada, Mexico, Singapore, and Switzerland allow authorisation reports issued by selected foreign agencies to be considered for the assessment of medicines for marketing authorisation (Luigetti et al., 2016^[38]). For example, SwissMedic takes into consideration assessments made by countries with comparable regulatory systems (e.g. assessments by the EMA and NRAs from EU countries) if the applicant requests it. This policy option has expedited the availability of medicines in the Swiss market by reducing the review time by 20% (Luigetti et al., 2016^[38]). Health Canada may use, when appropriate, assessments and reviews from other countries for background information, or as part of the evaluation process of generic medicines. These assessments can be used as a basis for regulatory decisions (Luigetti et al., 2016^[38]).

The ACSS Consortium is a collaborative initiative of like-minded, medium-sized regulatory authorities from Australia, Canada, Singapore, and Switzerland. The Consortium consists of several working groups that aim to help meet the challenges faced by regulatory authorities, including timely access to safe therapeutic products within a limited resource capacity. The working groups use a network of bilateral confidentiality agreements and Memoranda of Understanding to conduct their work. The ACSS Generics Medicines Working Group is currently trialling a work-sharing model based on the EU decentralised procedure. The ACSS NAS (New Active Substance) Working Group (previously known as New Chemical Entity working group) has also launched a work-sharing pilot for the coordinated assessment of a NAS application that has been filed in two jurisdictions. The pilot established a framework to understand the practicalities of undertaking a coordinated assessment that complemented the regulatory decision-making within each jurisdiction. The initiative represented a unique global collaborative effort between regulatory authorities and the pharmaceutical industry, which was able to streamline internal procedures for using international assessment reports and produced significant benefits for the pharmaceutical industry, through a reduction in regulatory burden and efficiency gains that contributed to advancing regulatory innovation (TGA, 2019^[44]).

In Singapore, the NRA also has a system called the 'Verification Route' that considers assessments completed by reference agencies (EMA, FDA, Health Canada, TGA in Australia, and the Medicines & Healthcare Regulatory Agency in the United Kingdom). In the 'Verification Route', for a product which has obtained a marketing authorisation by any two reference agencies, processing time can be reduced from 270 to 60 days (Luigetti et al., 2016^[38]).

Mexico has agreed on recognition of GMP information with the EMA and holds recognition agreements with Canada and the FDA for the regulation of medicines and the verification of medicines' production (Gonzalez Pier and Barraza Llórens, 2011^[35]; Sravani et al., 2017^[45]).

Other international collaborations have led to the increase of countries' NRAs' capacity. For example, in the Caribbean Community and Common Market (CARICOM¹¹), the Caribbean public health agency developed the Caribbean Regulatory System (CRS). The CRS helps states perform key regulatory activities by conducting abbreviated reviews of product dossiers for safety, quality, and efficacy of medicines that have current approval from a reference regional National Regulatory Authority (NRA/RR) (which includes the NRAs of Argentina, Brazil, Canada, Chile, Colombia, Cuba, Mexico, and United States) and is included in the WHO's Essential Medicines list or in PAHO's Strategic Fund.¹² CRS also provides benefits to the industry by offering a central portal for access to CARICOM's markets (CARPHA, 2018^[46]).

11 CARICOM includes Antigua and Barbuda, Bahamas, Barbados, Belize, Dominica, Grenada, Guyana, Haiti, Jamaica, Montserrat, Saint Lucia, St Kitts and Nevis, St Vincent and the Grenadines, Suriname, and Trinidad and Tobago.

12 PAHO's Strategic Fund is a regional cooperation mechanism of pooled procurement of essential medicines and health supplies

Where does Chile stand on international collaboration?

Chile is part of the Pacific Alliance. The Pacific Alliance, in its pharmaceutical chapters, seeks the harmonisation of regulatory agencies in Chile, Colombia, Mexico, and Peru, in particular to develop uniform guidelines and other regulatory mechanisms across these countries. Additionally, ISP and Mexico's COFEPRIS have been pursuing an agreement to harmonise requirements for, and regulatory aspects of the production of medicines; this agreement also seeks to achieve the mutual recognition of marketing authorisation, GMP certification and inspection visits (Srivani et al., 2017^[45]). More recently, a similar process of mutual recognition of GMP has been advanced with Colombia.

In the Americas, PAHO has established the Pan-American Network for Drug Regulatory Harmonization (PANDRH). Participants in PANDRH include the national authorities of countries in the Americas, and various pharmaceutical interest groups, industry, and academia. PANDRH seeks to establish technical guidelines for the harmonisation of processes as well as programmes for the NRA strengthening through training programmes. It is formed by 12 technical working groups, each with its own set of guidelines, addressing GMP, Bio-equivalence and Bioavailability, Good Clinical Practice, Drug Classification, Counterfeit Drugs, Good Laboratory Practices, Pharmacopoeias, Medical Plants, Drug Registration, Pharmacovigilance, Vaccines, and Promotion and Marketing (Lakkis, 2010^[39]).

PAHO and the PANDRH can further assist Chile in pursuing the harmonisation of regulations, improving capacity, and maintaining ISP's Level IV classification.

4.4. IMPLEMENTATION ACTION PLAN – IMPROVING THE REGISTRATION PROCESSES FOR MEDICINES

Chile's ISP has been classified as a level IV NRA, proficient and efficient in carrying out its regulatory functions of evaluating the efficacy, safety, and quality of medicines, and is considered a reference NRA by PAHO (Peña Ruz, 2010^[11]). However, like any NRA, ISP can encounter challenges in its functions that could be addressed through a number of strategies. These include updates to priority lists and abbreviated procedures; enhanced capacity and strengthened regional and international regulatory cooperation.

POLICY ACTION 1:

Continue updating priority lists for the marketing authorisation of generic medicines complying with requirements to demonstrate therapeutic equivalence.

In order to provide expedited approval procedures for certain generic medicines, Chile currently has in place a list of originator medicines whose respective generic copies are required to demonstrate bio-equivalence by 2021. Therefore, by 2021, all medicines included in these lists will have to certify bio-equivalence, with the timeline specified by Decrees 112, 115 and 117, and Supreme Decree 3. While it might be difficult to conduct these tests (many of the listed medicines are not available in the country, and are hard to find abroad), this regulation could be strengthened to clarify that all generic medicines should be therapeutic or bio-equivalents of their originator product (and not only the ones in the list), and that the current list is, in fact, a priority list.

The list should be updated to take into consideration the available products in the market (e.g. number of competitors for a specific medicine), public health needs (e.g. burden of disease in Chile, patients/users organisations), the requirements of the public sector (e.g. medicines procured by CENABAST and MINSAL programs). The list could also be developed in consultation with the pharmaceutical industry to take into consideration their projections, capacity, and challenges for meeting the bio-equivalence requirements for marketing authorisation.

Objective:

- Promote the availability in the market of generics of assured quality, safety, and effectiveness in the market.

Actions:

- Regularly update Decrees 112, 115 and 117 to take into account new products losing market exclusivity.

Timeframe:

- The issuance of a law that regulates operators' appeals should ideally take no more than one year. If instead, this mechanism is adopted through resolution, this process should take a maximum of six months.
- Amendments to the regulations should take one year.
- The development of priority lists should be an ongoing process until all medicines in the market have complied with therapeutic equivalence studies.
- The priority lists should be updated on an ongoing basis and should be revised every year.

Institutions/stakeholders involved:

- ISP
- MINSAL
- Generic Pharmaceutical Industry
- Pharmaceutical Industry Associations

Policy instrument:

- Upcoming Pharmaceutical Law 2/Pharmaceutical Law 1
- DS 3/2010
- Technical Norm 131

Milestones, indicators and evaluation:

- Generic medicines in the market as a share of the medicines in the priority list
- Number of marketing authorisation of medicines complying with therapeutic equivalence
- Compliance of therapeutic equivalence studies according to set timeframes
- Comparison of number of generic medicines in the market (that have complied with therapeutic equivalence studies) against the listed medicines

POLICY ACTION 2:

Continue revising the abbreviated procedures (proceso de registro abreviado and the proposed proceso de registro acelerado) to further prioritise new products with high public health value for access to any type of abbreviated evaluation process.

To further develop and implement the abbreviated registration process (fast-track, *proceso de registro abreviado*), it is important that clear regulations and guidelines indicate which medicines are eligible for it (i.e. how to determine if a medicine addresses a serious condition or unmet medical need) (Liberti et al., 2016^[17]), as well as the benefits that this process would bring to applicants (besides shorter approval times).

Furthermore, there should be dedicated resources for the evaluation of these applications and for managing dialogue with the applicant. Meetings with applicants are encouraged to discuss ISP expectations and requirements, and to provide assistance with clinical trial development and clinical data reporting. Furthermore, the proposed amendment of DS No. 3/2010 (*proceso de registro acelerado*) should include provisions that ensure effective and timely communication between the ISP and the industry, so that medicines registered under the accelerated procedure can fully benefit from it and medicines addressing unmet medical needs get to patients faster.

The regulatory process for the registration of medicines includes an Assessment Commission formed by members of the Pharmacology Society. External collaborators, such as universities, Clinical Research Organisations (CROs),

international organisations, etc., can be invited to contribute to this process as “Verification Units”, after ISP’s certification, to enhance and facilitate the assessment of these new technologies and to support abbreviated marketing authorisation procedures for new medicines. The certification of these external collaborations should include provisions that specify roles, responsibilities, and activities of all stakeholders involved; it should also be stated that these external collaborators are accountable to ISP and not the industry. Regulations and contracts between public and private institutions should include provisions to guarantee full transparency and disclosure of all relevant information, as well as provision to identify potential conflict of interest.

Objective:

- Further develop and implement the abbreviated assessment procedures to facilitate the early market entry of medicines addressing unmet medical needs with high public health value.

Actions:

- Amend relevant regulation (DS 3/2010, DS 54/2019) to define and expand the criteria to identify medicines that can undergo abbreviated and accelerated registration procedures (i.e. medicines that address unmet medical needs; that are considered innovative and of public-health interest; that are the first generic/biosimilar in the market; that are included in MINSAL programmes, or procured by CENABAST).
- Develop guidelines for the industry to consider and apply for this type of assessment, in addition to guidelines and criteria to provide the justification to include medicines under the abbreviated assessment.
- Establish a standing committee specialised in the assessment of upcoming medicines to regularly define/update whether they are eligible for an abbreviated or accelerated assessment. This committee should consider the inclusion of external experts.
- Have in place trained and specialised staff to address industry’s questions during the process, and to carry out the evaluation and authorisation procedures.

Timeframe:

- Amendment of the regulations should start as soon as possible and take no longer than three to four months to be approved, after which the standing committee should be set up.
- The development of guidelines should parallel the amendment of the regulations.

Institutions/stakeholders involved:

- The Ministry of Health, with the advice from ISP, should identify the main health issues and medical needs, and inform ISP about which should be prioritised.
- Industry should be consulted by the ISP during the development of guidelines
- Civil society (e.g. professional organisations, patient organisations) should be consulted in the definition of criteria for prioritisation.

Policy instrument:

- DS 3/2010 as it defines the abbreviated registration procedures, which is to be amended.
- New or updated guidelines and norms for this evolving procedure.

Milestones, indicators and evaluation:

- Number of new medicines eligible for this registration pathway.
- Time taken for marketing authorisation.
- Market surveillance of these products.
- Feedback from stakeholders about the process and how to improve.

POLICY ACTION 3:

Increase application fees for marketing authorisation to mobilise additional resources that can be used to ensure adequate human resources at ISP, while strictly avoiding any conflict of interest. Reassess ISP's technical capability and capacity building needs, anticipating technical skills needed for new and emerging technologies.

Evidence suggests that the human resources available for medicine evaluation in Chile are much more constrained than those of other countries, including those with comparable income levels. These limitations can create inefficiencies in regulatory processes. Therefore, building on international experiences, Chile could raise its user fees to better reflect the costs of evaluating applications and enhancing the capacity of the ISP to effectively and efficiently perform its functions. The size of the fee increases should be carefully evaluated and explained to stakeholders, highlighting the positive impacts for citizens and industry.

In parallel, maintaining the legitimacy of the whole process and all actors is central for the success of this policy. Citizens and all stakeholders must trust in the institutions in charge of marketing authorisations; therefore, transparency and avoidance of conflict of interests must be considered as well.

Within ISP's yearly activity planning, continuous training and professional development activities for staff should be factored in, in order to develop and maintain the level of expertise necessary for technically competent and timely regulatory tasks (Ratanawijitrasin and Wondemagegnehu, 2002_[22]). This could include formal training programmes for evaluators, in the form of attendance at external courses, or in-house and on-the-job training (Al-Essa, Salek and Walker, 2012_[47]). In-house training should be developed by the ISP in collaboration with academic institutions and other relevant stakeholders (e.g. international organisations) and be kept up to date (Ratanawijitrasin and Wondemagegnehu, 2002_[22]). This training and capacity building should foster an organisational culture that prioritises the protection and advancement of public health (Matsebula, Goudge and Gilson, 2005_[23]) and encourages the timely assessment of medicines (Ratanawijitrasin and Wondemagegnehu, 2002_[22]). The technical capacity of ISP can also be enhanced through the use of external experts or committees to assist with the assessment of applications. ISP currently has assistance from the Pharmacology Society.

Objective:

- Leverage revenues from the new user fees for marketing approval applications to increase and strengthen ISP's human resources and in turn improve approval times and processes.¹³

Actions:

- Conduct a financial evaluation of the additional resources needed to achieve full cost recovery for the evaluation of applications for marketing authorisation, including the cost of recruiting and training evaluators. This financial evaluation would be conducted jointly with MINSAL, the National Budget Office (Dirección de Presupuestos, DIPRES) and the Ministry of Finance. In particular, the assessment should include regulatory provisions regarding the use by ANAMED (National Medicines Agency) of the potential new resources coming from fees, their introduction into the general budget of ISP, compliance with the rules of public budget expenditure, and the eventual expansion of positions to hire new personnel in ANAMED ("dotación").
- After the financial evaluation and the required institutional changes assessment, start a dialogue with industry and consumer associations to communicate benefits and potential impacts of enhanced capacity for ISP. The dialogue could be conducted through a multi-stakeholder working group that would receive updates on the financial evaluation.
- Approve a resolution/decreed establishing the new user fees for marketing approval applications.
- Develop a strict plan aiming to enhance transparency and continuously assess and prevent any conflict of interest with industry and other relevant actors.

¹³ Similar recommendations were made by Chile's competition agency recently. See (Fiscalia Nacional Economica, 2020, pp. 234-235_[7])

- Develop yearly activity plans that consider human resources and capacity, the yearly projections of activities, and the qualifications of the staff. The plans could feed into the financial evaluation.
- Develop career plans for staff members that include ongoing training to develop qualifications, skills, and experience. This should consider time and financial resources to ensure that staff members maintain their knowledge and skills as advanced as possible in subject area which is rapidly evolving.
- Develop training programmes and/or promote the attendance of training programmes provided by academia, international organisations, and other relevant entities by staff.

Timeframe:

- The financial evaluations regarding user fee increases could be done over the course of three months, while the multi-stakeholder dialogue, the approval of the new resolution and the transparency and conflict of interest plan could take place in the medium/long term.
- Training should be an ongoing process. Staff members should receive training at least once a year to stay up-to-date with latest methods, and with information related to pharmaceuticals and other medical products.
- New staff members should receive intensive introductory training during the first 3 to 6 months of their employment.
- The training programme should be developed within 6 to 12 months, and updated and revised at least every year or when necessary (to start as soon as possible).

Institutions/stakeholders involved:

- ISP:
 - The Finance department can lead the financial evaluation of user fees.
 - The Human Resources department can have a unit responsible for developing and providing training courses, and/or finding external courses for staff to attend.
- MINSAL, in coordination with DIPRES and the Ministry of Finance, to advocate and support the user fees and regulatory update process and the ongoing training elements.
- Academia, public sector experts, international organisations and similar entities that can provide independent training on new pharmaceuticals, technologies and medical products.
- Industry, to adapt to the new user fees.

Policy instrument:

- ISP's internal regulations and functioning.
- Resolution/decree.

Milestones, indicators and evaluation:

- New user fees to achieve full cost recovery published and enforced.
- Plan for transparency and avoidance of conflicts of interest published and enforced.
- All new staff should comply with the required training within the first 3 or 6 months of their employment.
- Training programme should be periodical for both staff and their managers, with at least one update training a year.
- Monitor financial balance of ANAMED activities.
- The training programme should include provisions to evaluate the performance of staff members.
- Completion of required training by all staff and compared to their performance.

POLICY ACTION 4:

Develop and strengthen international collaboration, building on existing relationships with other regulators in the Latin American region, and expanding to other agencies. Work towards adoption of harmonised procedures and explore capacity for work-sharing.

Chile could pursue greater engagement with regional NRAs, such as ANVISA (Brazil), ANMAT (Argentina) and INVIMA (Colombia), which have been classified (together with ISP) as regional reference authorities for medicines by PAHO (PAHO, 2018_[111]). Harmonisation requires the formation of networks among regulatory authorities to build capacity and trust between agencies to facilitate the sharing of best practices, making the best use of finite resources and potentially reducing or eliminating duplication of effort (Al-essa, 2011_[40]). This would require, in the medium term, the standardisation of technical requirements for medicines regulation (Al-essa, 2011_[40]) and the adoption of the Common Technical Document (CTD), with eventual progression to the electronic implementation (eCTD). CTD implementation would facilitate the standardisation and evaluation of dossiers by ANAMED, streamline the application preparation for manufacturers, and facilitate work-sharing and document exchange with other regulators. Harmonisation and collaborative work-sharing will be subject to reaching agreements on information sharing. This has been developed in the Resolution No. 2233 of September 14 2020 of the ISP, which approved the format for the submission of background information for pharmaceutical products registry applications, taking as a reference the international standard of the CTD.

Chile could also consider joining the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) as an observer (thereby gaining an opportunity to participate in the evolution of harmonised evaluation procedures), as well as the International Coalition of Medicines Regulatory Agencies (ICMRA). The ICMRA is a coalition of regulatory authorities that work together to address regulatory challenges, provide direction for areas and activities common to many regulatory authorities, and promote synergy and collaboration among NRAs, to leverage existing efforts to maximise global impact (ICMRA, 2017_[48]).¹⁴ ICMRA provides a platform to support enhanced communication, information-sharing and crisis response. It also focuses on strengthening regulatory systems and capacity (Skerritt et al., 2015_[49]).

Objective:

- Strengthen the capacity of ISP and facilitate the application process for new medicines through stronger international collaboration and engagement.

Actions:

- Introduce the electronic CTD (e-CTD) (to follow the introduction of CTD), after an assessment of financial needs by MINSAL and DIPRES.
- Continue pursuing harmonisation of pharmaceutical regulatory aspects and regulations within the Pacific Alliance countries.
- Consider amendments to procedures and regulations to harmonise regulations with those of other NRAs of the region.
- Consider technical advice and guidance from PAHO/PANDRH to reach regulatory harmonisation and strengthen international collaboration (to start dialogue with PAHO as soon as possible).
- Consider joining the ICH as an observer
- Consider joining the International Coalition of Medicines Regulatory Authorities (ICMRA)

¹⁴ There are two types of members: full members and associate members, which should commit to supporting the activities of the ICMRA and sharing information. Associate members receive all documents generated by the ICMRA and are invited to join working groups; associate members can attend meetings but do not have a vote and are not entitled to attend meetings. Full members must appoint an Executive Committee to manage activities of the ICMRA and appoint a chair and vice-chair; the membership approves and endorses projects according to strategic aims; full members commit to support the ICMRA activities, share information, and have a vote on resolutions and decisions taken at the ICMRA. ICMRA meet at least 4 times per year. Countries interested in becoming associate members can write to the secretariat indicating their interest to join ICMRA; these countries will be requested to submit an expression letter to the secretariat that includes: competencies, size of their authority, areas of international interest and existing international initiatives, capacity and interest in contributing to ICMRA, and details of any existing agreements in place (ICMRA, 2018_[113]).

- Explore interest in and capacity for work sharing with regional regulators, to be preceded by a period of confidence building and pilot assessments.

Timeframe:

- Consolidate use of the common technical document (CTD) as a short-medium term priority.
- Two to three years to revise regulations, assess differences and similarities, identify areas of improvement and action, and amend regulations as appropriate.
- Exploration of work sharing could be undertaken over the same period.
- Start discussion on joining ICMRA as soon as possible.

Institutions/stakeholders involved:

- ISP.
- MINSAL.
- PAHO/PANDRH.
- Regional NRAs.
- Ministry of Economy

Policy instrument:

- DS 3/2010.
- Pharmaceutical Law 1.
- Technical Norm 131.
- Guidelines from PANDRH.
- Pacific Alliance agreements and statutes.

Milestones, indicators and evaluation:

- Amendment to regulations to enable adoption of harmonised procedures, work-sharing and implementation of CTD and eCTD.
- Adoption and full implementation of CTD.
- Implementation of eCTD.
- Establishment of arrangements for document sharing with other NRAs.
- Establishment of arrangements for work-sharing with other NRAs.
- Reduced marketing authorisation approval times. Expedited entry of products whose evaluation has involved work sharing or document exchange with other NRAs.

POLICY ACTION 5:

Expedite marketing authorisation procedures by expanding mutual collaboration around assessments of other NRAs and exploring information sharing and mutual recognition mechanisms. This could range from the sharing of evaluation reports with independent decision-making to mutual recognition of other agencies' decisions.

International regulatory cooperation; adoption of harmonised processes and standards; and reliance and collaboration across NRAs can all help leverage capacity and improve regulatory efficiency (Kaddu et al., 2018^[37]; OECD, 2018^[25]).

In addition to harmonisation and collaborative work-sharing, Chile could utilise (in whole or in part) evaluation reports prepared by other NRAs or the WHO as the basis of decision-making. These could also be utilised to support accelerated or abbreviated approval procedures (fast-track) in Chile. ISP officials pointed out that information provided by the industry on medicines already approved by the FDA and EMA was often summarised and outdated, and less detailed than the original submission presented to these agencies. ISP should consider

pursuing International Regulatory Co-operation Agreements (Kaddu et al., 2018^[37]) with these and other relevant agencies to obtain direct access to relevant, up-to-date, and complete information.

Chile has already moved forward with the approval of the Decree No. 54 of November 7 2019, which amended the decree No. 3 of 2010 of the Ministry of Health, approving regulations mainly to generate an accelerated registration procedure for those medicines that have already been granted marketing approval by a stringent regulatory agency. Efforts should move now to establish more stable and long-lasting engagement with these agencies, for instance, by sharing information with them on an ongoing basis.

A longer term option could be to pursue mutual recognition agreements with regional and/or like-minded regulators, such that marketing approval decisions made by one regulator within a consortium would be accepted and adopted by the others. This could be considered initially for generic medicines (though this would still require processes to ensure that the product being approved in Chile is identical in content and quality to that being approved by the other regulator), and perhaps also for new medicines of high public health interest. However, the industry may argue that this undermines the justification for increasing fees and charges.

Objective:

- Expedite marketing authorisation procedures by expanding collaboration in assessment, and adoption of decisions of other NRAs.

Actions:

- Adoption of mechanisms to enable sharing of information and mutual recognition of decisions of other like-minded NRAs (e.g. Latin American regulators) to expedite decision making in Chile. This can build on existing collaboration with agencies in the region.
- Regulatory instruments (e.g. 'reglamentos' guiding the assessment and approval of medicines) might have to be modified to allow the use of information sharing.

Timeframe:

- Consider a timeframe of two to three years to revise regulations, assess differences and similarities, negotiate agreements, identify areas of improvement and action, and amend regulations as appropriate.

Institutions/stakeholders involved:

- ISP.
- MINSAL.
- PAHO/PANDRH & WHO.
- NRAs of Latin American countries.

Policy instrument:

- DS 3/2010.
- Pharmaceutical Law 1/Upcoming Pharmaceutical Law 2.
- Guidelines from PANDRH and WHO.
- Technical Norm 131.

Milestones, indicators and evaluation:

- Amendment to regulations to permit decisions based on mutual recognition.
- Reduced marketing authorisation approval times.
- Monitor expedited entry of products for which decisions were based on assessment reports prepared by, or mutual recognition of decisions of other regulators.

A close-up photograph of two hands holding pills. The hand on the left holds a blue and white pill, while the hand on the right holds a red and white pill. The background is blurred, showing a person in a white lab coat.

5. State of play and challenges in Chile's generics market

5.1. STATE OF PLAY IN THE GENERICS MARKET IN CHILE

5.1.1. Ongoing reform of generic approval in Chile

Chile has recently decided to raise standards for the approval of generic medicines to align them with international norms. Before the implementation of generics policies in Chile, copies of originators in the market were pharmaceutical equivalents,¹ not necessarily therapeutic equivalents. This did not conform to international standards: providing evidence of therapeutic equivalence is a prerequisite for the marketing authorisation of generic medicines in most OECD countries to ensure that they provide the same therapeutic effects as their reference (originator) products (Kaushal et al., 2016_[50]). The objective of the new generics policy in Chile is to mandate therapeutic equivalence to facilitate generic substitution and provide confidence and transparency regarding the quality, safety, and efficacy of generic medicines (Morales, 2015_[51]) (see Box 5.1). However, it must be noted that some confusion still exists in the terminology of different regulations on this topic, with some regulations referring to therapeutic equivalence and some to bio-equivalence (see section 5.2.1.).

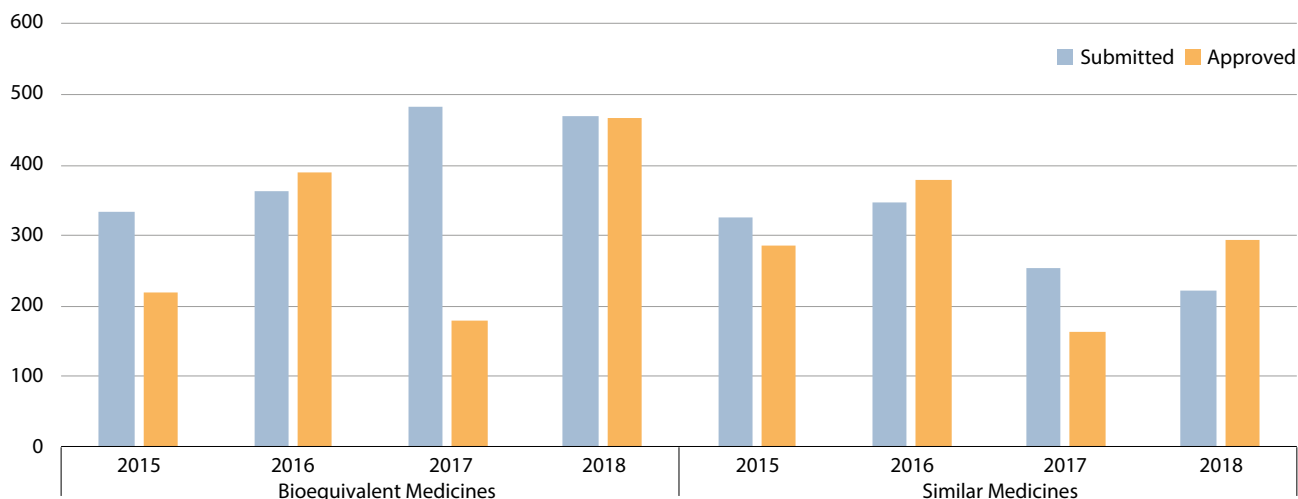
Chile has gradually implemented policies to improve the quality of generic medicines (Goldstein, 2018_[53]). Therapeutic Equivalence was introduced in 1997, and gradually advanced through other regulations until the consolidation of the policy on the interchangeability of medicines in 2014. A list of regulations and other relevant legislation is provided in Annex D. In 2014, the *Law on Pharmaceuticals 1* (Ley de Fármacos 1) was enacted. It regulates interchangeability and emphasises the importance of bio-equivalence in the assessment of efficacy and safety of generic medicines. To avoid major disruption in generic supply, the ISP/MINSAL requirements for bioequivalence were implemented gradually. Initially, the industry was given three years to comply by submitting bio-equivalence studies for those products included in a list specified by MINSAL and ISP. The deadline has since been extended and the current deadline to comply with the law by submitting studies of therapeutic equivalence for listed products is 2021 (Ministerio de Salud, 2018_[54]).

In recent years, the number of pharmaceutical products that have demonstrated therapeutic equivalence through bio-equivalence studies has increased. However, this policy has not created an incentive for the entry of new generics, and in general has not been as successful as expected (Fiscalia Nacional Economica, 2020, p. 29_[7]). Despite an increase in the number of bio-equivalent products in market, shortages have been reported (Tobar et al., 2017_[55]; Goldstein, 2018_[53]). Moreover, despite the requirement for evidence of bio-equivalence a considerable number of similar medicines are still being registered without this (See Figure 5.1). ISP officials reported that while there are more approvals being granted for bio-equivalent medicines than similar medicines, nearly 60% of multisource medicines currently in the market have not yet demonstrated bio-equivalence.²

1. See glossary.

2. According to the FNE, only 20% of all generics available in the market have demonstrated therapeutical equivalence (Fiscalia Nacional Economica, 2020, p. 107_[7]).

Figure 5.1. A considerable number of similar medicines without certified bioequivalence are still receiving approval for marketing authorisation applications



Source: ISP officials.

To date, the ISP has registered over 2,150 products considered therapeutically equivalent. Of these, 1,921 products hold valid marketing authorisation and should be available in the market. 200 products are not available in the market.

In addition, the *Law on Pharmaceuticals 1* included provisions requiring prescribers to add the International Non-Proprietary Name (INN) to the brand name, and eliminating incentives for physicians to prescribe originator brands instead of generics (Goldstein, 2018). These incentives (known in Chile as “canela”) included money, donations, and services offered by pharmaceutical companies to prescribers and pharmacists to prescribe and dispense medicines of a certain brand (Goldstein, 2018^[53]).

BOX 5.1. REQUIREMENTS FOR DEMONSTRATING THERAPEUTIC EQUIVALENCE

In Chile, generic medicines must provide reports that establish therapeutic equivalence, either in vivo or in vitro, according to the criteria defined by the MINSAL standards (Ministerio de Salud, 2012^[52]). Products in solid pharmaceutical forms, for oral administration, immediate release, and products with the same active ingredient but different concentration can be eligible for a bio waiver to demonstrate therapeutic equivalence only if they are formulated with the type of active principle that meets the characteristics established by the biopharmaceutical classification system and found in the lists drawn up by the authority (Ministerio de Salud, 2012^[52]). The objective of bio waivers is to avoid unnecessary clinical trials in humans and expedite the demonstration of (in vitro) therapeutic equivalence.

For parenteral products formulated with very water-soluble active ingredients, the interchangeability is considered adequately assured through the implementation and certification of GMP, evidence of compliance with its quality specifications, and labelling according to regulations (Ministerio de Salud, 2012^[52]).

Bio-equivalence studies must be carried out in authorised clinical units. Clinical research organisations (CRO) can be contracted by the producer to perform bio-equivalence studies if they are certified by the ISP or by the WHO, the European Medicines Agency (EMA), and the NRAs of the USA, Canada, Spain, Japan, UK, Sweden, or Switzerland (Ministerio de Salud, 2012^[52]).

Annex E provides an international comparison of pharmaceutical equivalence studies to establish interchangeability of medicines and for marketing authorisation. These requirements and parameters apply to chemical entities only. The interchangeability of biological medicines (biopharmaceuticals or biosimilars) are not within the scope of this comparison. Interchangeability requirements for biosimilars should be considered in the regulation with corresponding and appropriate applicable studies and measures to demonstrate biocomparability.

For the countries compared in Annex E (Chile, Mexico, US, Brasil, EU countries and Australia), the following key insights can be extracted:

- In all countries, the NRA has regulations to determine reference medicines. The NRAs have developed and published lists of reference medicines to be used for interchangeability studies.
- Each country’s regulations define the requirements for establishing interchangeability. These countries have defined those medicines required to establish bio-equivalence, those that can apply for a bio waiver (in vitro studies), and those exempted from bio-equivalence studies as their pharmaceutical forms require other studies to demonstrate interchangeability.
- These countries have defined similar guidelines for the conduct of bio-equivalence studies and standard values and parameters to establish whether medicines are interchangeable or not.

If the physician adds the INN to the prescription, the pharmacist is allowed to substitute a generic for the originator, subject to the patient's agreement. If the prescribed medicine has no therapeutic equivalent, the pharmacist must supply the medicine as specified in the prescription (Ministerio de Salud, 2014^[56]).

Pharmacies are also required to have in stock a minimum number of medicines as indicated in the so-called "Pharmacy Request" (*Petitorio Farmacéutico*). The "Pharmacy Request" in DS 466 lists 244 medicines included in the national medicines formulary (Ministerio de Salud, 2018^[54]), which includes bio-equivalent medicines approved by the ISP. According to a study conducted in 2013, from 232 medicines listed by ISP as required to prove bio-equivalence, only 49 medicines are listed in the "Pharmacy request" (Departamento Políticas Farmacéuticas y Profesiones Médicas, 2013^[57]).

Another aspect addressed by the *Law on Pharmaceuticals 1* was communication with the public about the existence of bio-equivalent medicines in order to encourage their use. However, these campaigns have focused mainly on the impact of their availability on lowering prices and potential savings in out-of-pocket expenditure in medicines, rather than on reassuring the public about their safety and efficacy to improve trust in generic medicines (MINSAL, 2020^[58]). While patients continue to pay out of pocket for their medicines, there remains strong interest in lowering prices to promote affordability, especially in light of high health expenditure (see section 3.2.2).

Likewise, the law regulates the labelling requirement for all bio-equivalent medicines to increase their visibility. The regulations require all bio-equivalent medicines to use a specific logo and other packaging specifications to make the product more recognisable (see Figure 5.2).

5.1.2. Market shares of generics in Chile

Generic market shares in Chile are quite high by international standards, with 84% by volume and 64% by value of sales in retail pharmacies (see Figure 5.3). Given that most medicines sold to hospitals are copies of originator products, the actual generic market share for the whole market in volume is likely to be higher.

The differential between market shares in volume and value suggest that the price differential between originators and copies is lower in Chile than in many countries. This might be due either to high generic prices or to low originator prices. Unfortunately, no recent price comparison enables to confirm any of these hypotheses. Another possibility is that this differential can be explained by price differences between branded and unbranded products – regardless of whether they are original products or generics. Between 2015 and 2018, a branded product was sold at three times the price of unbranded products, even as this disparity has been on a downward trend: from branded products being over 3.5 times more expensive than unbranded ones in 2015, to only 2.5 times more expensive in early 2019 (Fiscalia Nacional Economica, 2020^[7]).

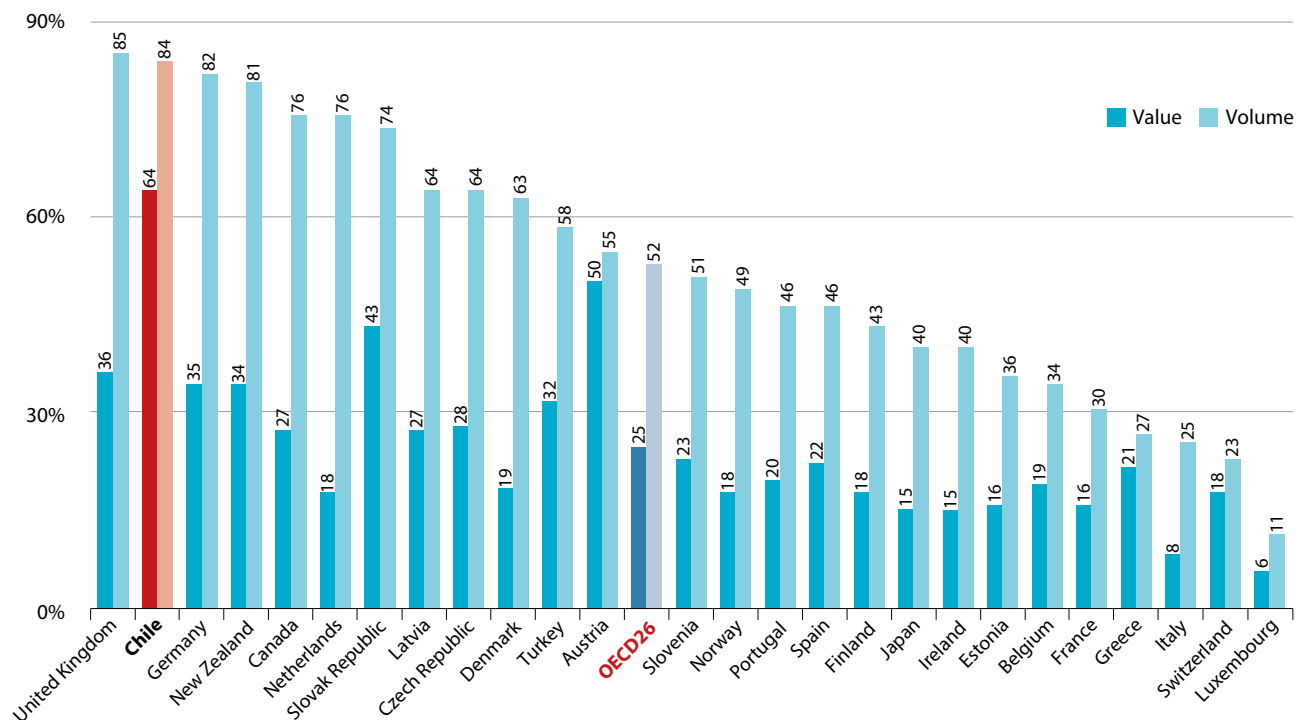
Overall, between 2000 and 2018, generic market shares in Chile have increased from 56.8% to 63.6% by value and from 77.7% to 84.5% by volume (see Figure 5.4).

Figure 5.2. Packaging and labelling of bio-equivalent medicines



Figure 5.3. Chile has one of the highest share of generics in pharmaceutical markets across OECD countries (2017 or latest available year)

For Chile, all types of copies of originators are included in the 'generics' categories, regardless of requirements for marketing authorisation. Data only cover sales in retail pharmacies

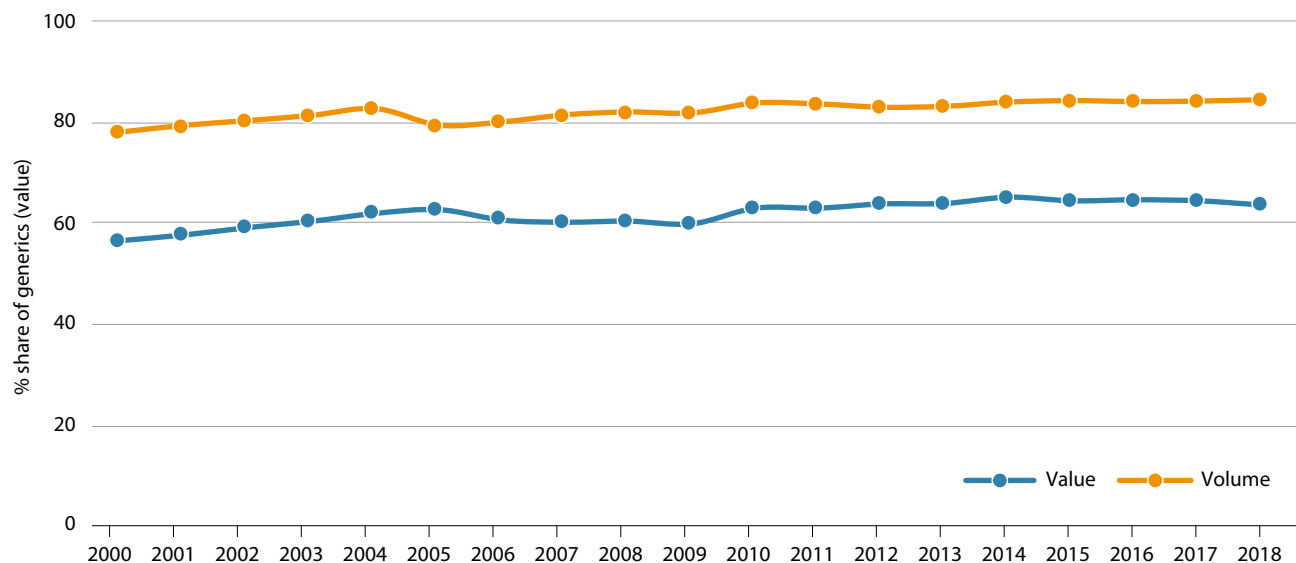


Note: 1. Reimbursed pharmaceutical market. 2. Community pharmacy market.

Source: OECD Health Statistics 2019.

Figure 5.4. Generic uptake in retail pharmacies in Chile has increased, 2000-2018

For Chile, all types of copies of originators are included in the 'generics' categories, regardless of requirements for marketing authorisation. Data only cover sales in retail pharmacies



Note: Volume is a number of boxes.

Source: OECD Health Statistics 2019.

5.2. CHALLENGES IN CHILE'S GENERICS MARKET

5.2.1. Challenges in the implementation of regulatory reform

The implementation of the 2014 generics policy in Chile required that selected products demonstrate bio-equivalence by 2021 in order to obtain or retain marketing authorisation (Tobar et al., 2017^[55]). The implementation of this policy has also faced other challenges as described below.

Low compliance

The pharmaceutical industry claims that the implementation of this policy lacked flexibility regarding timelines, and did not consider the capacity of the industry to comply with the requirements (Tobar et al., 2017^[55]). Many producers failed to comply within the three-year timeframe and have been subject to sanctions, in accordance with Exempt Decree No. 27 (FNE, 2013^[58]), which required them to cease distributing their products in the market. However, if they later present the necessary studies to establish bio-equivalence they can obtain marketing authorisation and resume supply. To date, only 43% of those medicines required to demonstrate bio-equivalence have had studies submitted to ISP. As a result, some medicines have no or very few bio-equivalent options available, thus limiting competition and generic substitution (SERNAC, 2018^[59]; Kaplan et al., 2019^[60]).

ISP capacity

The implementation of the policy did not ensure the adequate capacity of the ISP to process the marketing authorisation applications of all products, or take into account the implications for the supply of medicines or the availability and update of reference products lists (Tobar et al., 2017^[55]). This situation has reduced generic options in the market, undermining competition and potentially affecting prices (SERNAC, 2018^[59]).

Confusion in terminology

The World Health Organization (WHO) uses the term multisource medicine to refer to a medicine that can be purchased under several trademarks from different manufacturers or distributors. These multisource medicines may or may not be therapeutic equivalents.

Therapeutic equivalents are those that have the same or comparable quality, safety, and efficacy specifications as their reference products, have been shown to be bio-equivalent, and are referred to as generic medicines (Homedes and Ugalde, 2005^[61]; World Health Organization, 2006^[62]; González, Fitzgerald and Bermúdez, 2007^[63]).

DS 3/2010 defines pharmaceutical equivalents as “pharmaceutical products containing identical amounts of the same active ingredients or salts or esters thereof, and having the same pharmaceutical form and route of administration, but not necessarily the same excipients, and meeting the same or similar quality specifications”. It also defines a therapeutic equivalence study as “a comparative clinical, bioavailability, pharmacodynamic or “in vitro” test performed on a reference pharmaceutical product and another one under evaluation” (Ministerio de Salud, 2011^[64]).

Within the regulatory framework, different instruments use different terminology. For example, DS 3/2010 refers to studies to demonstrate therapeutic equivalence, while the *Law on Pharmaceutical 1* refers only to bio-equivalence. That said, several regulations (Resolución Exenta No. 727, Resolución Exenta No 4886, DS 3/2010, Pharmaceutical Law 1, etc.) define pharmaceutically equivalent and therapeutically equivalent products (Ministerio de Salud, 2011^[64]; Ministerio de Salud, 2012^[52]).

In the distribution chain, three types of multisource medicines are commonly distinguished, even though they are not specifically defined in the regulations (Fiscal Nacional Economica, 2018^[65]):

- Branded Similar (Similares de Marca) are copies of originator medicine, which are marketed with a brand name.
- Pharmacy-Own-Branded Similar (Similares de Marca Propia) are branded similars, which are marketed by a pharmacy that is vertically integrated with the manufacturer.

- Generics (*Genéricos*) are medicines commercialised using the name of the active principle (INN) only.

Medicines belonging to these categories *may or may not have demonstrated bio-equivalence* to the originator product, depending on whether their active substance was included in the list.

Governments in the present decade have launched public awareness campaigns about the benefits of bio-equivalent products, mainly focusing on prices and potential savings for consumers (Balmaceda, Espinoza and Diaz, 2015^[66]; Goldstein, 2018^[53]). These campaigns have confused the public regarding bio-equivalent medicines and substitution policies (Tobar et al., 2017^[55]), even though bio-equivalent medicines are required to be packaged and labelled in order to be easily recognisable (see Table 5.1).

Table 5.1 Relevant terms used to describe generic medicines, as defined by the WHO and Chile's regulations

Term	WHO Definition*	ISP Definition**
Pharmaceutical Equivalents	Medicines are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards. Pharmaceutical equivalence does not necessarily imply bio-equivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and absorption.	Pharmaceutical products containing identical quantities of the same active ingredients or their same salts or esters, presented in the same pharmaceutical form and route of administration, but which do not necessarily contain the same excipients and which comply with the same or comparable quality specifications.
Therapeutic Equivalence	Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate bio-equivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.	Pharmaceutical equivalents that comply with the same or comparable quality specifications and that when administered according to the conditions specified in its labelling, their effects, with respect to efficacy and safety, are essentially the same, all determined by appropriate studies. ³
Bio-equivalence through bioavailability studies	Two medicinal products are bio-equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.	The bioavailability studies are pharmacokinetic studies that through a pre-established experimental design allow the determination of the bioavailability of an active principle. Bio-equivalence is established through comparative bioavailability studies
Multisource medicines	A medicine that can be purchased under any of several trademarks from different manufacturers or distributors. When the patent of a medicine expires, a single-source medicine becomes multisource. Multisource medicines are intended to be pharmaceutically equivalent or pharmaceutical alternatives that are bio-equivalent and hence are therapeutically equivalent and interchangeable.	Medicines that are pharmaceutical equivalents, which may or may not be therapeutic equivalents. If they are required to be interchangeable, they must demonstrate therapeutic equivalence and meet the same quality standards as the reference product.
Generic medicines	Multisource pharmaceutical products that are therapeutically equivalent and thus are interchangeable, not taking into consideration of whether or not the 'originator' molecule is, or was, under patent protection.	Not specifically defined in legislation

*WHOCC glossary (WHOCC PPRI, 2019^[67])

**ISP and Chile's regulations (Ministerio de Salud, 2011^[64]; Ministerio de Salud, 2012^[52])

Challenges*WHOCC glossary (WHOCC PPRI, 2019)

**ISP and Chile's regulations ((Ministerio de Salud, 2011; Ministerio de Salud, 2012b))

3 In Chile, generic medicines must provide reports that establish therapeutic equivalence, either *in vivo* or *in vitro*, according to the criteria defined by the MINSAL standards (Ministerio de Salud, 2012^[52]). (Ministerio de Salud, 2012b). Products in solid pharmaceutical forms, for oral administration, immediate release, and products with the same active ingredient but different concentration can be eligible for a biowaiver to demonstrate therapeutic equivalence, only if they are formulated with the type of active principle that meets the characteristics established by the biopharmaceutical classification system and found in the lists drawn up by the authority (see Table Annex B) (Ministerio de Salud, 2012). The objective of biowaivers is to avoid unnecessary clinical trials in humans and expediting proving (in vitro) therapeutic equivalence and marketing authorisation. (Saavedra et al., 2011). For parenteral products formulated with very water-soluble active ingredients, the interchangeability is considered adequately assured through the implementation and certification of GMP, evidence of compliance with its quality specifications, and labelling according to regulations (Ministerio de Salud, 2012^[52]). (Ministerio de Salud, 2012b).

Limitations on substitution

The *Law on Pharmaceuticals 1* introduced the concept of interchangeability to allow substitution of bio-equivalent medicines. However, the regulations only permit interchangeability between originator products and products that are therapeutically equivalent to them, and not between therapeutically equivalent copies (Goldstein, 2018^[53]).

5.2.2. Competition challenges in generic markets

Market studies are a powerful tool for competition authorities to examine broader competitive conditions in one or more sectors. The International Competition Network (ICN) defines market studies as “research projects conducted to gain an in-depth understanding of how sectors, markets, or market practices are working” (ICN, 2018^[68]). Fifty-eight of the 59 jurisdictions that participated in a 2015 OECD survey reported using market studies in some form in their work, suggesting they are a common instrument for competition authorities (OECD, 2017^[69]).

Market studies are an important tool to promote competition, even if they do not investigate illicit anti-competitive practices. In Chile, as elsewhere, such studies cannot result in the imposition of sanctions or compulsory measures. Instead, the Chilean competition authority – the *Fiscalia Nacional Economica* (FNE) has the possibility to make non-binding recommendations to public and private entities concerning the studied market.

The legal framework governing market studies in Chile was amended in mid-2016, when FNE was granted explicit powers to conduct market studies and was provided with same information-gathering powers as those already available to it in its competition investigations. Among these powers, the most relevant for market studies are the power to request information from companies and to interview any person the FNE deems necessary.

The result is that market studies prior to 2016 were not as comprehensive or in-depth as those pursued since then. Between 2012 and 2016, the FNE pursued a number of market studies into the pharmaceutical sector. These looked into: (i) the private health market; (ii) bio-equivalence and generic entry; (iii) tender processes for prescription drugs in the public health sector; and (iv) the supplemental protection of patented drugs. Currently, an in-depth study into the pharmaceutical sector is being pursued by the FNE. Since this market study benefits from the 2016 legal reform, it is expected that it will benefit from much more nuanced and granular information than previous studies, and will lead to a more sophisticated understanding of the sector than what was previously possible.

Bio-equivalence and generic entry

In Chile, several challenges prevent the successful promotion of bio-equivalent drugs and generic entry, as highlighted by several market studies.

Firstly, **uncertainty on the part of consumers** regarding the quality and / or effectiveness of bio-equivalent medicines poses significant obstacles to the successful entry of cheaper bio-equivalent products into the market, as confirmed by a market study on bio-equivalence and generic entry conducted by Chile in 2013. The perception of “lower quality” of generic drugs tends to act as a barrier to entry, an issue that hinders competition and generates artificially high market prices. This uncertainty encourages the use of brands as quality signalling tools – and leads to competition taking place on the basis of branding rather than price (Fiscalia Nacional Economica, 2020, p. 18^[7]). In effect, despite the prevalence of generic consumption in Chile noted above, around 70% of all medicines consumed (by unit), and 90% of all medicine expenses (by value) are devoted to branded products (Fiscalia Nacional Economica, 2020, pp. 110-111^[7]).

The use of originator brands as proxies for quality can distort the decisions made by consumers and avoid effective price competition, diverting the competitive efforts of companies towards other variables with greater impact but fewer benefits for consumers such as medical promotion, the provision of incentives to pharmacies, etc.

This analysis was supported by findings in a 2008 academic study that showed that branded generics were marketed at higher prices than unbranded generics in Chile, despite no evidence or regulatory controls that would allow one to establish that branded generics are safer or more effective than unbranded generics (Danzon, 2008^[70]). This study also found that Chile was one of the few countries in its sample, alongside Brazil and Mexico, where the prices of medicines

were higher than would be expected given their income per capita – and that this difference was at least partly a consequence of reduced competition arising from doubts about the quality of generic products (Danzon, 2008^[70]).

Secondly, **structural problems in the prescription and distribution of drugs** in Chile limit the freedom of choice by consumers and pose obstacles to generic penetration. A first problem is the lack of alignment of incentives for doctors and pharmacies to prescribe and dispense cheaper versions of a medicine (Fiscalia Nacional Economica, 2020, p. 18^[71]). A second problem is vertical integration or links between pharmaceutical companies and pharmacies that may lead the latter to promote original medicines.

To address these structural problems, mandatory prescription by INN for doctors and the right to substitute for pharmacists can be important solutions; as well as the implementation of effective incentive mechanisms so that consumers are able and willing to accept cheaper available versions of a multisource product. However, despite doctors already being under an obligation to use the INN in addition to the brand name when prescribing, the regime is ineffective – seemingly as a consequence of lack of monitoring and absence of effective sanctions (Fiscalia Nacional Economica, 2020, p. 18^[71]).

In addition, it is essential for pharmacies to be mandated to stock generics, and additional measures should be adopted to promote the consumption of generics and counterbalance potential distortions created by arrangements between entities at the various stages of the pharmaceutical distribution chain that create barriers to generic uptake. Such measures include more favourable reimbursement policies by insurers for patients who decide to purchase generic drugs, government campaigns that promote the consumption of generic drugs, and an obligation for pharmacies to substitute the medication prescribed with a lower priced therapeutic equivalents, among others.

Ultimately, **the low penetration of bio-equivalent drugs** in Chile shows the need for an integrated health policy that takes into account the various levels of the distribution chain, as well as both supply- and demand-side considerations.

Tender processes for prescription drugs in the public health sector

According to a market study carried out by the FNE in 2014, the tender terms and conditions used by public hospitals benefitted manufacturers of originator products, and blocked market entry of generics. This was considered inconsistent with the bio-equivalence policy that the Health Ministry was promoting at the time. The study suggested changes to the tender terms and conditions to allow more competition from companies that manufacture generic drugs.

Supplemental Protection of Patented Drugs

Competition challenges also exist regarding how long patents concerning prescription drugs would confer market exclusivity to those drugs in practice. A related market study was undertaken in 2016 by FNE and Chile's IP office (*Instituto Nacional de Propiedad Intelectual*, "INAPI"), which performed a legal analysis of the applicable rules. In particular, the FNE analysed the rules governing the supplemental protection period for patented drugs adopted in 2007, with the goal of extending the period of exclusivity in the market after patent expiry.

Under the terms of the 2007 reform, the protection period conferred by a patent begins from the moment the patent application is filed. To compensate for delays in the award of patent rights caused by the relevant administrative procedure, and given that the period of patent protection would be running during such procedure, the 2007 reform provided for a supplemental protection period for patents in addition to the normal statutory protection period.

However, the FNE found that supplemental protection was being granted also to patents issued under the earlier IP regime, despite those patents benefitting from a protection period that started to run from the date the patent was awarded. The FNE concluded that there was no justification for the award of supplemental protection to such patents, since in such a scenario the period of effective protection was not affected by the administrative procedures for the award of IP rights. The result of the award of supplemental protection to patents awarded under the earlier regime was that these patents would be able to enjoy three more years of patent protection without justification, allowing originators to prevent timely market entry and price-lowering competition.

The FNE looked at 12 medicines sold by nine manufacturers which were protected by a patent granted under the pre-2007 regime but which had nonetheless been granted supplemental IP protection. It found that this extension of the period of IP protection led to over 11 billion pesos in extra expenditures. Given that there had been hundreds of applications for supplemental protection, it was likely that the harm caused by these rules was substantially higher than this amount.

To remedy this issue, the FNE recommended that the law should be amended to preclude patents obtained under the earlier patent regime from benefitting from supplemental protection. An alternative would be to adopt an interpretation of the rules governing supplemental protection in line with the goal of the provisions, which would have an effect similar to the proposed legal reform.

Pharmaceutical Market

A FNE market study pursued at the same time as this assessment looked to identify further competition challenges. This is the first market study of the pharmaceutical sector to be pursued under the new regime. Given the much more extensive information-gathering powers that the FNE now possesses, the study looked at the pharmaceutical market as a whole and benefited from previously unavailable information.

The study was launched in April 2018, and the final report was published in January 2020. The Report looks at the whole production, distribution, dispensation and retail chain for medicines, and also analyses how demand for medicines works.

Its launch was justified by concerns already identified in earlier market studies, and others that arose in the context of investigating competition infringements in the sector. These include the artificial extension of IP protection for pharmaceutical products, the poor design of medicine tenders by hospitals and other institutional channels, the imperfect implementation of bio-equivalence policy in the country, the high concentration observed in the pharmaceutical retail market, and the lack of alignment of pharmacists' and physicians' incentives with those of consumers.

5.3. GOOD PRACTICES IN OECD COUNTRIES

5.3.1. Good regulatory practices

Clear definition of generic medicines

A key difference between Chile and other countries is the lack of a clear definition of generic medicines (see Box 5.2). Mexico, the United States, Australia, and the EU define generic medicines as pharmaceutical equivalents of originator medicines that have provided evidence that they are also therapeutic equivalents. These countries require that all multisource medicines – products in the off-patent market – are therapeutic equivalents, and thus suitable for substitution at the point of dispensing.

While regulations require that all copies of originators must demonstrate bio-equivalence to enter or remain in the market, for now only listed medicines are required to do so. Regulation DE No. 115/2018 (Ministerio de Salud, 2018^[54]) has updated the list of medicines that must demonstrate bio-equivalence within a certain timeframe, with the result that similar and unbranded products already in the market all have deadlines by which to submit bio-equivalence studies. Currently, 60% of the follow-on medicines in the market are yet to demonstrate bio-equivalence with their originator products, but all must do so by 2021.

Limiting the types of pharmaceutical products in the market

For small molecules⁴, OECD countries generally have two types of medicines in their market: originator products and generics (Tobar, 2008^[71]). Generics are required to demonstrate therapeutic equivalence with the originator product in order to be approved, and may or may not carry brand names (Enríquez Rubio et al., 2005^[72]; FNE, 2013^[58]).

4 For biologic products, there are also biosimilars.

Instituting mandatory therapeutic equivalence has been achieved in a number of countries, including in South America. In Mexico, for example, the main generics policy strategy consisted of amending the National Health Law (*Ley General de Salud* – LGS) and the Regulation of Health Products (*Reglamento de Insumos para la Salud* – RIS) to convert all multisource medicines to interchangeable generic medicines in the market (Enríquez Rubio et al., 2005^[72]; Hayden, 2007^[73]). Prior to this amendment, Mexico also had several types of multisource medicines that included interchangeable and non-interchangeable generics (Barraza Llórens and Guajardo Barrón, 2013^[74]). Changes in the legislation required all copies of medicines to submit interchangeability studies (Enríquez Rubio et al., 2005^[72]). This requirement applied both to new products and already registered products, which had to submit interchangeability studies within 5 years in order to renew their marketing authorisations. These changes eliminated non-interchangeable generic medicines from the market. As a result, the pharmaceutical market now consists only of originator medicines and interchangeable generic medicines marketed either with brand names or their INN.

In 1999, the Ministry of Health of Brazil enacted the Generic Drug Act. This legislation required bio-equivalence to be established as a prerequisite for marketing authorisation (Massard Da Fonseca and Shadlen, 2017^[75]). At the time, three types of pharmaceutical products were available: originators (or reference) products, similar medicines (not interchangeable with a reference product, but using the same INN), and generic medicines (interchangeable with reference products, with their own brand name). Since doctors were expected to prescribe using the INN, consumers were allowed to choose among these three types of products (Da Fonseca, 2014^[76]). In 2004, the Brazilian regulatory agency requested that all similar medicines become bio-equivalent by 2014 (Resolution 133 and 134/2003 of the Generic Drug Act (Law 9787/1999)) (Valente, 2006^[77]). Although there are still a few non-bio-equivalent similar medicines in the market, most similar medicines are now bio-equivalent (Massard Da Fonseca and Shadlen, 2017^[75]). To promote the interchangeability of generic medicines, the agency has encouraged collaboration with the national generics industry, by providing consultation and support to assist them in meeting the bio-equivalence requirements (Massard Da Fonseca and Shadlen, 2017^[75]), alongside a ‘fast-track’ regulatory process.

BOX 5.2. DEFINITIONS OF GENERIC MEDICINES IN DIFFERENT COUNTRIES

Chile

In Chile, there is no legal definition of the word ‘generic’ and the common use of this term is at odds with international usage (see §4.2.5). Copies of originator products that have demonstrated therapeutic equivalence to their originator products exist in the Chilean market and are what other countries refer to as generics.

Brazil

In Brazil, according to Resolution RDC nº 135 of May 29, 2003¹, generic medicines are defined as medicines that are similar to a reference or innovative product, which is intended to be interchangeable with, usually produced after the expiration or waiver of patent protection or other exclusive rights, proven to be effective, safe and of good quality, and designated by the Brazilian common denomination (DCB) or, in its absence, by the international non-proprietary name (INN).

Mexico

Generic medicines are pharmaceutical products complying with interchangeability tests showing that these are equivalent with respect to the reference product. All medicines destined for the generic market shall be interchangeable.

United States

A generic product is expected to be: pharmaceutically equivalent to its reference listed product, bio-equivalent to the reference product, and therapeutically equivalent, i.e. to be substitutable for the reference product with the expectation that the generic product will have the same safety and efficacy.

European Union

A generic medicinal product is a medicinal product with the same qualitative and quantitative composition as the reference product, the same pharmaceutical form, and whose bio-equivalence with the reference product has been demonstrated.

Australia

A generic medicine is a medicine that, in comparison with a registered medicine:

- Has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the registered medicine or previously registered medicines; and
- Has the same pharmaceutical form; and
- Is bio-equivalent.

1 Retrieval at: https://www.cff.org.br/userfiles/file/resolucao_sanitaria/135.pdf

Source: Based on each country’s applicable regulations (see Table 4.1. and Annex B)

5.3.2. Market structures and incentives at play in OECD countries

The impact of supply and demand in the distribution of pharmaceuticals

The market for pharmaceuticals has some characteristic features that have important implications for the types of regulation and market structure that are most conducive to comprehensive coverage, lower prices and efficient outcomes.

Demand for a number of pharmaceuticals is rather inelastic, because the one who makes the decision about the purchase (the doctor) is not the one who pays (the consumer or the insurer), and, hence, is less sensitive to price and often less informed about it. In addition, pharmaceuticals are credence goods. Consumers require specific knowledge to determine when and how they should be used. As a result, consumers typically cannot choose autonomously which medicines to buy.

Even doctors suffer from asymmetries of information, and rely considerably on manufacturers to obtain information on the effectiveness of drugs. Pharmacists may be in a similar position, as they often have a role in influencing the decision of consumers, especially when regulation requires or allows them to substitute the products prescribed by the doctor with cheaper alternatives.

Because manufacturers can manipulate this distribution system, and because of the lack of alignment of incentives for doctors, pharmacies and patients/payers, it is a common practice for countries to regulate the content, quality and reliability of the marketing information received by the different actors, for example by setting minimum standards (e.g. provision of truthful and not misleading information; balance of risks and benefits). Similarly, it is common to regulate the types of incentives that manufacturers can provide to doctors and pharmacies (OECD, 2014^[78]).

Once a patent expires, generic versions that contain the same active ingredient can enter the market. These generics undergo a much leaner authorisation procedure than their originator reference products. Moreover, most jurisdictions actively promote access to, and consumption of generic drugs, which are usually much less expensive than their branded counterparts (OECD, 2018^[79]).

When there is limited information on the quality, safety and efficacy of the generics, consumers can perceive originators to be more effective and reliable than subsequent "cheaper copies", and be resistant to the use of generics, especially unbranded ones (which are the cheapest). In addition, physicians may themselves not trust generics, often due to lack of reliable information on their bio-equivalence, may not be aware of their availability, or could be reluctant to switch when already prescribing an originator. Hence, a combination of lack of reliable testing requirements, ignorance, risk-aversion, and resistance to change weakens the degree of competition that generics can generate. (OECD, 2014^[78]).

As a result of this demand inelasticity, attention is being placed on the demand side of the market, and regulations aimed at providing incentives to doctors, pharmacists and patients to pay more attention to the financial costs of their choice have been introduced in many countries. Information campaigns and/or policies and regulations aimed at ensuring the provision of clear and understandable information to consumers on the quality, safety and effectiveness of generics can help dispel any conscious or unconscious biases towards 'cheaper medicines' as being inferior. This would in turn facilitate better responsiveness to price signals and incentives.

Table 5.2. Mechanisms to increase responsiveness to prices

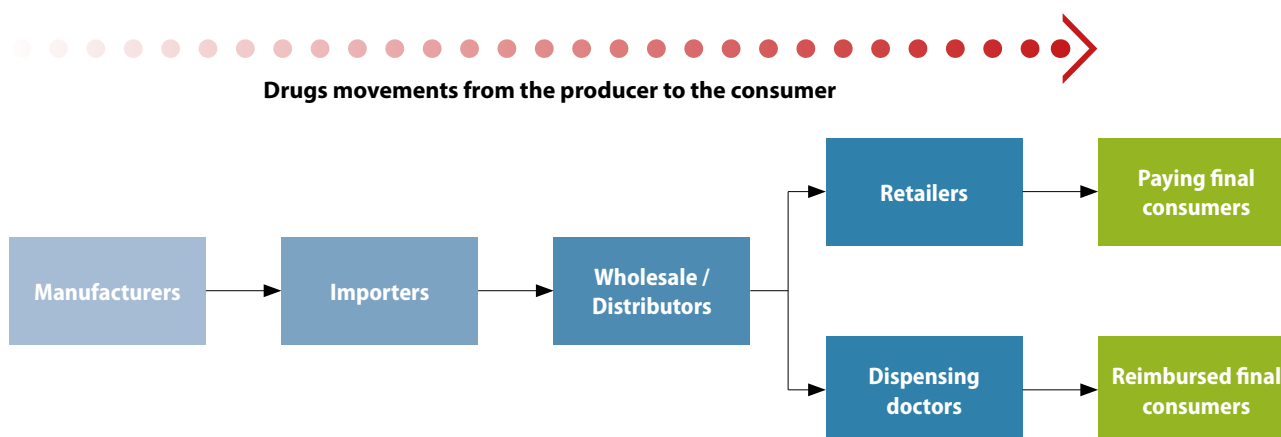
Mechanisms to increase responsiveness to prices	
Consumers	Co-payments
	Financial incentives for purchase of lower cost drugs, such as: – offering consumers a lower co-payment if they accept a generic version of the prescribed drug – limiting the reimbursement amount to the cheapest generic version of the drug
Physicians	Salient, easy to understand information
	Voluntary or mandatory prescriptions by INN rather than by brand name
	Financial incentives for prescribing generics rather than originators
	Pharmaceutical budgets, coupled with financial incentives
Pharmacists	Benchmarking of physicians' prescribing patterns, coupled with financial incentives
	Voluntary or mandatory substitution by generic or lower-cost medicines
	Margin regulation: – Mark-ups are often regressive in relation to the price of drug – Payment might be disconnected from the price (e.g. dispensing fee)
Insurers/payers	Bulk-buying
	Tenders to procure drugs directly from manufacturers
	Formularies and discount for drugs flagged as “preferred drugs” (which incur lower co-payments)

Pharmaceutical distribution

Each of the characteristics discussed above may not only affect outcomes in pharmaceutical markets, but can also influence the effectiveness of certain market structures for the distribution of pharmaceuticals. This can explain why the distribution of pharmaceuticals follows different models in different jurisdictions, and even within jurisdictions, as is the case in Chile.

Any intervention at one level of the distribution chain must take into account potential impacts on other levels of the chain – i.e. interventions should be holistic and take into account the pharmaceutical market as a whole. This is because, interventions at each level of the distribution chains – e.g. to address increased concentration in a specific level – can have knock-on effects on other levels of the chain, and have unintended implications for the ultimate effectiveness of the distribution chain, the consumption of pharmaceuticals and their final price (OECD, 2014_[78]).

Figure 5.5. A typical distribution chain



Source: (OECD, 2014_[78])

The main players in a typical pharmaceutical distribution chain are:

- **Manufacturers** – Manufacturers can be located in the country of final sale, or in other countries, reflecting increasing concentration and globalisation of the industry. “In Chile, the production of medicines can only be conducted in pharmaceutical laboratories especially authorized for this purpose by the ISP, which must also supervise and control them (Fiscalia Nacional Economica, 2020, p. 59_[7]). Despite a large number of laboratories in the country, markets for individual medicines are very concentrated as a result of the market structure at this level. From the point-of-view of the final consumer, 72% of all medicines, amounting to 34% of all sales by volume, are produced by a single laboratory that provides them in the retail sector, which leads to very high market concentration in medicine markets (Fiscalia Nacional Economica, 2020, pp. 120-121_[7]). From the doctor's perspective, who prescribes and can choose between therapeutically equivalent commercial products, the market is still very concentrated, albeit less than for consumers, as 54% of all therapeutically equivalent medicines, amounting to 14% of all sales by volume, are produced by a single laboratory (Fiscalia Nacional Economica, 2020, p. 123_[7]).
- **Importers** – Sometimes these are large national wholesalers, sometimes firms specialising in obtaining the drugs from foreign manufacturers and selling them to local wholesalers. If drugs are manufactured outside the territory where they are sold and consumed, importers can play an important role in the distribution chain. Imports also happen when drugs are sold at different prices in neighbouring countries and, hence, arbitrage is possible, even taking into account the costs of transporting and selling goods across borders (a phenomenon known as ‘parallel imports’). This is something that Chile could benefit from, given that its prices are higher than those in neighbouring countries (Fiscalia Nacional Economica, 2020, p. 29_[7]). However, parallel import into Chile could have an impact on the prices charged in these neighbouring countries – in all likelihood, by leading to increased prices there.
- **Wholesalers and distributors** – Since retailers/pharmacies are generally too small to stock all the drugs they may require, wholesalers bulk-buy drugs from manufacturers and resell them in smaller quantities, ensuring regular delivery of drugs and providing related services (WHO and HAI, 2011_[80]). In a growing number of countries, wholesalers have become mere distributors with no direct ownership of the goods and no financial relationship with the retailers.
- **Retailers/Pharmacies** – Retailers (i.e. pharmacies) are those entities that obtain medicines from wholesalers, or directly from manufacturers, and dispense them to consumers. In some countries, there are public and private pharmacies that cater for different consumers: public pharmacies provide free or subsidised medicines, while private pharmacies only cater for paying consumers.

Pharmacy margin regulation tries to achieve a number of different objectives, often simultaneously. Constraints on margins are used as a tool to limit final prices, as consumers may not always be very price sensitive. They are also used to provide incentives to pharmacists for substituting high-priced medicines with generics/lower cost ones. In addition, margins may be regulated to ensure sufficient profits to pharmacies located in poorer or less densely populated areas.

Companies operating in the distribution of pharmaceuticals can operate at only one of these levels. However, it is common for companies to pursue a number of these roles simultaneously – an instance of what is called “vertical integration”. Vertical integration can take many forms. In some cases, a manufacturer may be integrated with a distributor or even with a retail pharmacy chain. In some cases manufacturers may team up together to set up a joint distributor that deals only with their brands.

Vertical integration may have an efficiency justification, as it may generate a number of benefits for the integrated entity: (i) cost savings from consolidating and rationalising certain activities; (ii) reduction in information asymmetries; (iii) elimination of double-marginalisation, and (iv) reduced risk of free-riding on investments. However, vertical integration can also have anticompetitive effects, in that it can reduce intrabrand competition or foreclose entry. In Chile, a recent study by the competition authority (FNE) found that vertical integration does not pose significant problems. First, even for integrated retail chains, only a minority of medicines sold are those that result from its

vertically integrated structure (from 2% to 9% of sales) (Fiscalia Nacional Economica, 2020, pp. 172-175^[7]). Second, the markets for vertically integrated products are not particularly concentrated, indicating that competitors are able to participate in these markets and are not foreclosed (Fiscalia Nacional Economica, 2020, pp. 177-179^[7]).

Conclusions and policy options

Different organisational models are possible for the distribution of pharmaceuticals, with uncertain impact on final consumer prices and welfare. In effect, the impact of certain distribution structures on final prices will depend on the specific market conditions and applicable regulatory framework (OECD, 2014^[78]). This is particularly apparent in Chile, where different types of distribution structure and levels of vertical integration have been adopted by individual players.

A particular implication of this complexity is that any intervention at the relevant stage of the supply chain that does not take into account its impact on other levels of the supply chain – and on the different business models of market players in Chile – is likely to have unintended consequences.

As a result, any potential intervention in the market for the distribution of pharmaceutical products must start from a detailed analysis of the actual conditions in the Chilean market, the potential pro- and anticompetitive effects of potential changes by reference to the status quo, and the role that the regulatory framework plays in framing competition and setting prices in Chile.

A good example of how complex these effects can be is provided by a recent market study, which found that prices paid by retail pharmacies were 70% higher than those paid by the public sector for the same products, and 60% higher than those of institutional purchasers (mainly clinics) (Fiscalia Nacional Economica, 2020, pp. 129, 133^[7]). It was further found that this did not relate to volume differences (Fiscalia Nacional Economica, 2020, pp. 131-134^[7]). It would seem that retail pharmacies pay more – and hence charge more – because they prefer to acquire a variety of branded products, while institutional health providers bid for individual classes of products and display greater willingness to purchase non-branded products. This, in turn, reflects information asymmetries regarding the quality of medicines that lead pharmacy consumers to prefer branded products – leading those pharmacies to stock those products. (Fiscalia Nacional Economica, 2020, pp. 15-17, 139-145^[7])

The implication is that retail pharmacies do not charge higher prices solely as a result of their market power, even though this may be an explanation for part of their margins.⁵ Instead, another plausible explanation for the high prices of medicines sold by retail pharmacies is the preferences of their customers, who choose not to buy unbranded generics when paying for their medicines out-of-pocket. To address this, solutions should not focus on altering the market structure, but rather on incentivising greater acceptance of generics on the part of customers.

5.3.3. Good practices to encourage generic substitution

To promote and facilitate generic substitution, several countries have developed reference lists that provide relevant information about generics with marketing authorisation in the country to inform healthcare professionals and consumers about generic alternatives in the market. The United States (Orange Book), the United Kingdom, Finland, Sweden, Japan, Brazil, and Mexico are examples of countries that have developed such reference lists (González, Fitzgerald and Bermúdez, 2007^[63]; Hassali et al., 2014^[81]; Jakovljevic, Nakazono and Ogura, 2014^[82]).

In the United States, for example, once a generic medicine has been granted marketing authorisation, the product is incorporated into the 'Orange Book', which is regularly updated by the FDA (González, Fitzgerald and Bermúdez, 2007; Hassali et al., 2014). The Orange Book, whose official publication name is "Approved Drug Products with Therapeutic Equivalence Evaluations" serves as a guide to interchangeability as it contains information on medicines approved by the FDA and their approved generic equivalents. The Orange Book provides information and advice to the public, to practitioners, and to the states regarding medicines selection and generic substitution (FDA, 2018^[83]).

5. Which have increased in recent years – see (Fiscalia Nacional Economica, 2020, p. 163^[7]).

Table 5.3 Policy tools to promote the use of generics in OECD countries

	Prescription in INN			Generic drug substitution			Incentives to prescribe/ dispense /purchase generics		
	Not allowed	Allowed	Mandatory	Not allowed	Allowed	Mandatory	Incentives for pharmacists	Incentives for patients	Incentives for physicians
Australia		X			X		F	F	–
Austria	X			X			–	NF	NF
Belgium		X		X			NF	F	F&NF
Canada ¹		X ¹	X ¹		X ¹	X ¹	F ¹	F ¹	¹
Chile			X ²		X		–	F	NF ²
Czech Republic		X			X		n.a.	F	F
Denmark		X				X	NF	F	NF
Estonia		X				X	–	NF	NF
Finland		X				X	NF	F	NF
France			X		X		F	F	NF&F
Germany		X				X	NF	F	F
Greece		X			X		–	F	NF
Hungary		X			X		NF	F	F
Iceland					X		n.a.	F	n.a.
Ireland		X			X		NF	F	NF
Italy		X				X	NF	F	NF
Japan		X			X		F	F	³
Korea		X			X		F	F	n.a.
Luxembourg		X		X			n.a.	NF&F	NF
Mexico			X		X			F	NF
Netherlands		X			X		F	F	n.a.
New Zealand		X			X ⁴		F	F	NF
Norway		X			X		F	F	NF
Poland		X			X		NF	F	–
Portugal			X		X		N	NF&F	N
Slovak Republic		X				X	NF	F	NF
Slovenia			X		X		NF	NF	NF&F
Spain		X				X	NF&F ⁵	NF&F	NF&F ⁵
Sweden		X				X	NF&F	F	NF
Switzerland		X			X		F	F	–
Turkey		X			X		n.a.	F	–
United Kingdom		X			X		F	–	NF
United States ⁶							F ⁶	F ⁶	–

Note: F = Financial incentive; NF = Non-financial incentives; n.a. = information not available. For pharmacists, this table only considers incentives provided by drug coverage schemes. Market incentives (such as rebates from manufacturers, vertical integration, etc.) are not reported.

1. In Canada, the regulation of prescription and generic drug substitution differs across provinces and territories. Incentives for doctors, pharmacists and patients vary across drug plans.

2. Only in the public sector for medicines that are dispensed in public facilities.

3. In Japan, there is no direct incentive for physicians, but an incentive for medical institutions exists. Generics prices are revised after market entry.

4. If the pharmacist has a substitution arrangement with the prescriber.

5. In some regions.

6. Legislation on prescription in INN and substitution is not uniform across states. Incentives for pharmacists, patients and doctors vary across drug plans. Patients' co-payments are generally lower for generics.

Source: (OECD, 2017^[87]).

Furthermore, other countries have developed online platforms that allow the public to access information on pharmaceutical products available on the market, including prices. In Colombia, the Ministry of Health hosts a platform called the “Price Thermometer” (“Termómetro de Precios”) that allows the public to compare the prices of all generic products available on the Colombian market (MINSALUD, no date^[84]). Likewise, Peru’s “Price Observatory” (“Observatorio de Precios”) provides information on prices of generic medicines available in the Peruvian market as reported by private pharmacies; however, these prices serve as reference and might be different at the time of purchase (Ministerio de Salud, no date^[85]). In Argentina, the National Price Vademecum (Vademecum Nacional de Precios) is an official source of price information of medicines in the market, where the public can check relevant data of a pharmaceutical product available in the Argentinian market, including its price (ANMAT, 2019^[86]). These platforms seek price transparency, assisting consumers in making informed decisions regarding the purchase of medicines, and promoting the generic market.

Generic uptake and competition can also be enhanced by financial incentives for physicians to prescribe by INN, for pharmacists to substitute the cheapest generic, and for consumers to accept generic products. Almost all OECD countries have adopted such incentives, at different degrees (see Table 5.3).

Building on insights from the behavioural sciences and field trials, it is possible to identify a number of promising approaches to improving physicians’ decisions on prescribing, better informing consumers, and ultimately enhancing the quality and the cost-effectiveness of care. Tables 5.4 and 5.5 below provide an overview of strategies that have shown potential to change prescribing behaviour and promote better understanding among consumers of the benefits of generic medicines.



Table 5.4. Behavioural Strategies to Increase Prescription of Generics among Physicians

Defaults	<p>Make INN prescribing the default. A simple change to prescription default options in electronic medical records softwares immediately increased INN prescribing rates from 75 percent to 98 percent in a field experiment in the outpatient clinics of the University of Pennsylvania Health System (Patel, 2016_[88]).</p>
Prompts	<p>Changing the prescribing landscape. The use of electronic prescribing per se can increase the rate of generic medicine utilisation by giving physicians immediate access to a formulary as well as information on available generic options of all prescribed medicines including information on drug prices. This allows physicians to evaluate the treatment costs and discuss alternative choices with patients during the consultation (Ross, 2005_[89]); (Tseng, 2016_[90]).</p> <p>Adapting the choice architecture (i.e. “the context in which people make decisions” (Thaler, 2013_[91])). Having the INN available as the first choice, only requiring selection to compose the prescription, may increase the prescription of generics, but also generate significant cost-savings (Fischer MA, 2008_[92]).</p>
Saliency	<p>Redesigning the interface to emphasise INN prescribing. In a study by (Stenner SP, 2010_[93]), researchers discovered a positive impact of having generic formulations appearing as bolded and brand name medications appearing below the generics in a slightly smaller, unbolded font. In the study, the interface was specifically designed so that prescribers could still use the words they were accustomed to using to search for medications (ie, brand names), but the result of the search would present them with a list of options in which generic equivalents would be most salient– thus reminding providers of the availability of alternatives to the brand drugs they would usually prescribe. The intervention proved successful at increasing generic uptake and effects remained strong even two years after the intervention.</p>
Simplification	<p>Providing a simplified drugs summary list for the most common drugs used in primary care can significantly hasten the process of the physician checking for the INN during consultation, particularly given that poor routine and lack of time are common reasons for inappropriate prescribing (Mastura, 2008_[94]).</p>
Feedback	<p>Peer comparison. Audit and feedback to healthcare professionals on whether their clinical practice is consistent with that of their peers or accepted guidelines can be effective in improving professional practice (Jamtvedt G, 1997_[95]); (Wadland et al., 2005_[96]).</p> <p>Opportunity cost. Feedback to resident and faculty physicians on estimates of cost savings that might have been realised by prescribing generics can significantly increase rates of INN prescribing by physicians (Gehlbach SH, 1984_[97]).</p> <p>Personalised information. Receiving personalised information regarding individual, team and health district prescribing behaviour, coupled with updated cards on generic drugs, clinical outreach and specific prescribing goals can increase INN generic prescribing by 15% (López-Picazo, 2002_[98]).</p>
Educational Outreach and Academic Detailin	<p>Academic detailing, a face-to-face encounter between the prescriber and a detailer with the aim of transferring unbiased information, has been shown to be effective in modifying physician prescribing behaviour (Doyne et al., 2004_[99]).</p> <p>Group detailing is particularly valuable as it has the advantage of encouraging discussions within the group, thus increasing the diffusion of the information across the social group and increasing the impact.</p> <p>Effective academic detailing initiatives to improve INN prescribing have a number of key elements (Soumerai SB, 1990_[100])</p> <ol style="list-style-type: none"> 1. conducting interviews to investigate baseline knowledge and motivations for current prescribing patterns, 2. focusing programmes on specific categories of physicians as well as their opinion leaders, 3. defining clear educational and behavioural objectives, 4. establishing credibility through a respected organisational identity, referencing authoritative and unbiased sources of information, and presenting both sides of controversial issues, 5. stimulating active physician participation in educational interactions, 6. using concise graphic educational materials, 7. highlighting and repeating the essential messages, 8. providing positive reinforcement of improved practices in follow-up visits.

Table 5.5. Behavioural Strategies to Increase Demand and Familiarity of Generics among Consumers

Framing	<p>Test different framings to increase trust in generics. Behavioural research shows that presenting choices in a way that highlights the positive or negative elements of the same decision can lead to changes in their relative attractiveness – what is commonly defined as the <i>framing effect</i> (Kahneman, D., & Tversky, A, 1979^[101]). In the context of health-relevant information, the evidence on framing suggests that messages which include references to potential gains or losses of a particular behaviour are better decision aids than no frame at all (Courtney MR, 2014^[102]). Thus when designing promotional materials for generics, it is worth testing different framing alternatives for public communication. Equally, emotional reactions to the general framing of generics could also be tested, e.g. to examine the relative impact of the terms “<i>bioequivalente</i>” and “<i>intercambiable</i>” in the Chilean market for drugs.</p>
Opinion leaders	<p>Using local opinion leaders to transmit norms and suggest appropriate behaviour may improve health professional practice. Six randomised trials of the use of local opinion leaders for health care outcomes showed that opinion leaders, alone or in combination with other interventions, may successfully promote evidence-based practice. Effectiveness can vary both within and between studies depending on context (Thomson et al., 1997) and the effect of using opinion leaders would need to be tested in Chile.</p> <p>Disseminating strategies. Informal one-to-one teaching sessions, community outreach educational visits, small group teaching, social media communications, academic detailing and trainings are examples of strategies used by opinion leaders for disseminating and implementing evidence-based practice (Flodgren G, 2011^[103]).</p>
Familiarity and cognitive ease	<p>Repetition of a message about generics through educational campaigns could increase familiarity and a feeling of cognitive ease. Cognitive ease results from a reduction in the perceived cognitive effort associated with a task, and it is likely to increase the acceptance of and preference for a message and product (‘exposure effect’) (Kahneman, 2011^[104]).</p>



5.4. IMPLEMENTATION ACTION PLAN: ENSURING BIO-EQUIVALENCE AND INTERCHANGEABILITY OF GENERICS

POLICY ACTION 6:

Continue developing all relevant regulations to require all copies of originator products to demonstrate bio-equivalence, and ensure that: a) no further products are granted marketing approval without evidence of therapeutic equivalence, and b) no further extensions are permitted for submitting evidence of bio-equivalence by listed products.

Currently, there are still lists of active ingredients for which all copies of the originator products have to demonstrate therapeutic equivalence to enter or remain in the market, with regulations allowing manufacturers considerable time in which to submit evidence of bio-equivalence, some until 2021 (Ministerio de Salud, 2018). This is the result of multiple extensions to the deadlines originally set for this transition. It is conceivable that manufacturers of some of these products will already have submitted bio-equivalence data in other countries; for others, there has arguably already been adequate time to arrange the necessary studies either in Chile or elsewhere. However, the amendment of regulations is necessary to request all copies of originator products in the market to prove therapeutic equivalence and thus become interchangeable.

Concerns have been raised that the requirement for bio-equivalence studies has been a driver of price increases seen in generic medicines, and one study suggested that the costs may have prompted the exit of some products from the market (Atal, Cuesta and Sæthre, 2018_[105]). Studies have reported poor availability and low market share of bio-equivalent generic medicines in the market (SERNAC, 2018_[59]; Atal, Cuesta and Sæthre, 2018_[105]).

While poor availability of bio-equivalent options in the market could undermine competition and inflate the prices of medicines, the mandatory nature of the demonstration of bio-equivalence promotes confidence in the quality of these products, thus fostering competition and lowering prices as a consequence (FNE, 2013_[58]). Although prices of some medicines did increase because of bio-equivalence studies, it is likely that in the longer term prices will decrease and will continue to do as more generics enter the market. It has been reported that when six or more generic products are available in the market, the impact of competition on the average prices of generics follows a descending pattern, with generic prices in Chile up to 39% lower than those of the originator products (Álvarez and González, 2018_[106]).

As such, Chile should adopt measures to ensure that the number of therapeutic equivalents available in the market increases (Fiscalia Nacional Economica, 2020, p. 233_[7]). The gradual implementation of therapeutic equivalence will require time, resources, and planning by ISP, and close collaboration with the industry to ensure the timely conduct of bio-equivalence studies, marketing authorisation, and availability of these medicines in outlets across the country. ISP could develop priority lists for evaluation based on the Chilean market requirements and public health needs (Kaplan et al., 2019_[60]), taking into consideration the plans, resources, capacity, and priorities of the industry to comply with this bio-equivalence requirement by 2021.

Furthermore, Chile could promote the development of more certified centres (CROs) for the conduct of bio-equivalence studies. Currently, there are 21 CROs conducting bio-equivalence studies and 22 CROs performing in vitro (bio-waiver) studies registered and certified⁶ by ISP in Chile. Promoting the development of new centres and the expansion of existing centres can assist the industry in fulfilling the 2021 requirements.

Objective:

- Ensure that there are only two types of medicines in the market: originators and generic medicines that have demonstrated therapeutic or bio-equivalence.

⁶ ANAMED's Biopharmacy and Bio-equivalence sub-department authorises and recognises Bio-equivalence and Biowaiver centres (CROs), including those recognised by stringent authorities. Studies carried out at these CROs follow ISP's regulations.

Actions:

- Check all relevant regulatory instruments to ensure consistency in terminology for originators and generics.
- Regularly update the priority list of medicines to demonstrate therapeutic equivalence.

Timeframe:

- The regulation establishes that multisource medicines should establish therapeutic equivalence as soon as possible. The current timeline should not be extended.
- Amendments should take a year to ensure that all regulations, decrees, etc. recognise and establish that all multisource medicines should be bio- or therapeutic equivalents.
- The list of medicines – the priority list of medicines to demonstrate bio-equivalence – should be developed and updated at least every 6 months.

Institutions/stakeholders involved:

- ISP.
- MINSAL.
- Pharmaceutical industry.

Policy instrument:

- DS 3/2010.
- Pharmaceutical Law 2.
- DS 115.

Milestones, indicators and evaluation:

- All documents should contain a statement that all multisource medicines should become therapeutic equivalents.
- All medicines applied for marketing authorisation, and all medicines on the market must have provided evidence of therapeutic equivalence.
- Monitor the number of medicines seeking marketing authorisation with evidence of therapeutic equivalence.
- Ensure there are no *similares* in the market or seeking marketing authorisation.
- Assess increase in the number of therapeutic equivalent medicines available in pharmacies.

POLICY ACTION 7:

Amend regulations to harmonise terminology within Chilean legislation/regulations and with international standards to reduce confusion during implementation of policy reforms. All regulations should use and refer to the same terms; their definitions should be the same across regulations and norms. In particular, the terms ‘generic’ and ‘interchangeability’ should be clearly defined, and aligned with international standards.

Clear and consistent definitions of terms are critical when setting out requirements and standards for medicines seeking marketing authorisation. Multiplicity and inconsistency in terminology can undermine the implementation of regulatory reforms and policy changes (Alfonso-Cristancho et al., 2015^[107]).

In Chile, the documents that regulate marketing authorisation (Pharmaceutical Law 1, DS 3/2010 and several other norms and decrees) use different terms to refer to generic medicines, therapeutic equivalence, and bio-equivalence, thereby creating confusion among stakeholders. Using the same terminology across regulations, legislation, and other relevant official documentation prevents confusion and can enhance the implementation of pharmaceutical policies. All documents, particularly the upcoming Pharmaceutical Law 2 (Ley de Fármacos 2), should refer to ‘generic medicine’, ‘multi-source medicine’, ‘therapeutic equivalence’, ‘bio-equivalence’, ‘originator medicine’, in a way that is consistent with international standards (see Box 5.1). Past regulation should be aligned with these standards where necessary. The term ‘generic medicine’ should be added to current legislation and regulation to refer to products, which have demonstrated therapeutic equivalence/bio-equivalence with the originator product.

Beyond clarifying Chilean legislation, the use of internationally agreed definitions has also the potential to facilitate import/exports and send clearer messages to consumers. Consumers need to understand that a generic approved in Chile is as reliable as a generic in the United States or in Europe. A similar development needs to happen regarding the terminology applicable to biosimilars in Chilean regulation. In the medium term, only three categories or medicines should exist in the market: originator medicines, generics, and biosimilars.

In parallel, the concept of 'interchangeability' should be clearly defined in legislation and regulation, as a prerequisite for the effectiveness of Chile's medicine substitution policy. Substitution of an originator by a generic, and substitution of one generic by another generic, should be possible and clearly understood by all stakeholders. It will be particularly important to ensure that any terminology used in communications with consumers conveys the message that generic and originators can be substituted. Terms, symbols and signs should be pre-tested.

The terms interchangeable or interchangeability can have a broader meaning, since evidence is often but not always obtained through bio-equivalence studies, which only refer to small molecules in solid presentations. This can create confusion for other types of medicines when seeking generic substitution (e.g. aqueous solutions, powders, creams, sprays, etc.) (Alfonso-Cristancho et al., 2015_[107]). Although Chile's regulations already contemplate bio-waivers and how other multisource medicines can demonstrate safety and efficacy, regulations should move forward into developing more specific guidelines for liquid formulations, emulsions, and topical products. Such reforms should strive towards interchangeability to promote generic substitution.

Objective:

- Clarify definitions of pharmaceutical products for all stakeholders and align them with international standards.

Actions:

- Scan legislation and identify all the terms that need to be harmonised, including 'bio-equivalent', 'generic' and 'interchangeability'.
- Amend the main regulatory instruments by using the agreed harmonised terms (to start as soon as possible and to align with Pharmaceutical Law 2).
- Test what would be the best term to use for prescribers, patients and the general population to communicate and educate about the use of generics. This term would replace the term 'bioequivalente', which is very technical. Using the word 'generic', as in many countries, is clearly an option.
- Design an information campaign that would inform consumers of the new terms and the generic options available to them. The information campaign could use innovative mechanisms for engaging consumers (including the use of social media). Messaging and provision of information should be pre-tested for clarity and intelligibility.

Timeframe:

- Start scanning legislation and testing appropriate terms as soon as possible. The new terms can be introduced in the Pharmaceutical Law 2, so the timeframe should be aligned with the times of the project of law in Congress.

Institutions/stakeholders involved:

- ISP.
- MINSAL.
- Chilean Association of Pharmacists.
- Practitioners/Prescribers (Chilean Medical Association (Colegio Médico) and Medical Societies in Chile).
- Consumers (consumers and patients' organisations).

Policy instrument:

- Pharmaceutical Law 2.
- Educational and informational campaigns.
- Regulatory instruments that use the main terms identified.

Milestones, indicators and evaluation:

- Terms identified and agreed in order to harmonise them in the regulation.
- Terms to be used with stakeholders and general population identified and agreed.
- Communication and informational campaigns in place.
- Knowledge and understanding of the new concept by stakeholders and general population.

POLICY ACTION 8:

Amend regulations to promote both prescription by INN and generic substitution.

In Chile, generic substitution occurs when patients request a generic option, and only for listed products that have demonstrated bio-equivalence. However, patients usually do not request generics and only request the product specified in their prescription (containing the brand name of the originator product), which may have a higher price than other available products (FNE, 2013_[58]). In fact, a recent survey found that 96% of all patients buy the exact product prescribed by a doctor (Fiscalia Nacional Economica, 2020, p. 18_[71]). In addition, over 35% of doctors are not convinced that, given Chile's bioequivalence policy, replacing a branded product with a generic is safe (Fiscalia Nacional Economica, 2020, p. 19_[71]). Since products in the market should be interchangeable (after demonstrating bio-equivalence or other), the pharmacists, prescribers, and costumers should be assured that all versions of a given product available in the market will provide the same desired therapeutic effect.

Prescribing solely by INN should be encouraged, as it has been already considered in the upcoming Pharmaceuticals Law 2. INN prescription promotes a more transparent and fair generics market, thus fostering competition. By using INN, prescribers do not influence the purchase of a product based on a brand preference, but focus instead on the medicine itself; therefore, INN prescription can reduce perception biases caused by marketing strategies of pharmaceutical companies (e.g. brand loyalty).

The prescriber's role in effective generic uptake should be addressed beyond compulsory INN prescription. Providing training and information on prices and cost-effectiveness of substitutes, and information on prescribing practices and behaviours that could harm patients, should be considered. It is important to bring doctors on board on the effective implementation of generic substitution (Kaplan, Wirtz and Laing, 2016_[108]).

INN prescription will allow pharmacists and patients to have more transparent discussions of consumers' preferences and convenience (e.g. procuring low-priced generics to reduce medicine expenditure by patients), and allow consumers to make more informed decisions when purchasing medicines.

It is highly recommended to enhance the pharmacists' role in generic substitution. Pharmacists should be trained in generic substitution, and should be requested to provide price information and information about generic options to patients to promote generic substitution.

Other barriers preventing effective generic substitution relate to patients' knowledge about the policy itself and/or the existence of interchangeable/bio-equivalent generics in the market (Kaplan et al., 2019_[60]). Therefore, it is also necessary to develop campaigns to inform the population about the existence of generics, assure them of their quality and other specifications, as well as their health and economic benefits, thereby seeking to address any concerns about the use of generic medicines (Hassali et al., 2014_[81]). Being informed about generic substitution will allow consumers to evaluate price against the benefits of different products (Kaplan, Wirtz and Laing, 2016_[108]). The consumers' role in generic substitution should not be overlooked.

However, generic substitution is only possible between interchangeable medicines – that is, between originators and medicines that have proven therapeutic equivalence. Therefore, INN prescription and effective generic

substitution can only be achieved once all generics in the market become therapeutic equivalent medicines and thus interchangeable with the originator product (Al-jazairi et al., 2008_[109]). For INN prescription to be effective, the terms and types of products in the market should be simplified and reduced to two only words: *originators* and (interchangeable) *generics* (branded or non-branded) as recommended.

Objective:

- Promote generic substitution and prescription by INN.⁷

Actions:

- Introduce mandatory prescribing by INN by amending regulations/implementing it through the Pharmaceutical Law 2. Prescribing by INN prior to patent expiry would also help prescribers and patients to focus on the active substance rather than the brand (to be reflected in the current discussion of the Pharmaceutical Law 2).
- Design communication and educational campaigns directed to prescribers to get them on board with INN prescribing. When developing these campaigns, consider:
 - Complementing them with **personalised feedback** to prescribers regarding their practice and how it compares to others (e.g. “most physicians prescribe generics”); how it compares with ideal cost-effective decision-making (e.g. “By prescribing generics, your patient would save X% or X amount”). Feedback messages could be tested through an experiment to ensure that they are well understood and effective.
 - Implementing them through face-to-face **academic or educational outreach** and unfolding them in the format of group discussions to ensure that the benefits of using INN are well understood.
- Design a communication and educational campaign directed at pharmacists. Require pharmacists to provide information to consumers/patients about generic options available and their prices.
- Design a communication and educational campaign directed at consumers/patients about the benefits of generic medicines to encourage them to request generic substitution. When developing these campaigns, consider employing **opinion leaders** to disseminate knowledge.
- Develop an electronic prescription system to support INN prescribing and promote generic substitution by pharmacists. The software should propose to replace any brand name with the relevant INN, and should list all medicines that are interchangeable. The system could be developed by a public or private entity, but the information base (e.g. the list of interchangeable products) should be unique and disseminated by health authorities (timeline to be discussed with key stakeholders to start design as soon as possible).⁸

Timeframe:

- Aligned with the adoption of Pharmaceutical Law.
- The development of an electronic prescription system would require careful design, learning from successful experiences and specifications for the developer. A timeframe of two to three years would be feasible to start pilots in selected ‘servicios de salud’.

Institutions/stakeholders involved:

- ISP.
- MINSAL.
- Chilean Association of Pharmacists.
- Practitioners/Prescribers (Chilean Medical Association (Colegio Médico) and Medical Societies in Chile).
- Consumers (consumers and patients’ organisations).
- Ministry of Finance and the National Budget Office (DIPRES) to define and approve the budget for the electronic prescription system.

7. Similar recommendations were made by Chile's competition agency. See (Fiscalia Nacional Economica, 2020, pp. 235-237_[7])

8. This is in line with the recommendation made by the FNE – see (Fiscalia Nacional Economica, 2020, pp. 26-27, 236_[7])

Policy instrument:

- Pharmaceutical Law 2
- Educational and informational campaigns
- Regulatory instruments to implement an electronic prescription system

Milestones, indicators and evaluation:

- Monitoring actual prescription by INN after implementation (referring to the brand name in brackets or not at all). This, however, would require access to information on prescribing, which is available in many OECD countries. In the absence of such information, a survey would be needed to monitor compliance with the obligation to prescribe by INN.
- Similarly, monitoring of generic substitution and purchases of medicines in the retail market would require survey data as there is no systematic collection of what is prescribed and what is dispensed.
- Out-of-pocket expenditure in medicines is only monitored at the macro-economic level through household surveys.
- Monitoring prices of medicines in the retail market.
- Reliance and trust in the use, quality, safety, and efficacy of generic medicines could be surveyed at regular intervals to monitor its evolution.

POLICY ACTION 9:

Develop and publish an updated list of multisource products that are interchangeable for the information of prescribers, pharmacists and the general public, and for integration into the electronic prescribing systems.⁹

Providing information to prescribers, pharmacists, and consumers can promote generic substitution and support well-informed decisions. An online platform could be developed and updated regularly with the most up to date information about new and generic medicines available in the market. The information contained in this platform should include the brand name of the originator product, together with information related to the quality, safety, and efficacy of the product; as well as the general availability of such products in outlets and pharmacies across the country (including pharmacy's contact information).

A further option for consideration, is for the Patent Office, alone or in conjunction with INAPI, to establish an easily accessible online resource of relevant pharmaceutical patent information for prospective generic manufacturers. Ideally this would include relevant patent expiry dates, which would assist generic manufacturers in determining when entering the market would be potentially put them at risk of patent infringement.

This platform could also include information on prices to help consumers making choices and increase price competition.

This platform should be readily available to pharmacies and their pharmacists to inform consumers/patients, in real time, about the generic options in the market, including their price. Since all medicines where generics are available should be interchangeable (therapeutic equivalents), consumers' decisions could be based on price. Having all information available in real time will allow consumers to make a more informed decision consistent with their ability to pay.

The development of this platform should be accompanied by active campaigns to inform prescribers, pharmacies, and the public about the existence of such a platform and the information it contains, and about the importance

9. Along similar lines, Chile's competition authority has recommended that it is of utmost importance to adopt clear public policies concerning the production, organisation and publication of information regarding medicines, in order to promote substitutability and market competition where possible (Fiscalia Nacional Economica, 2020, pp. 233-234₍₁₇₎).

and benefits of generic substitution. Having readily and reliable information on pharmaceutical products available in the market, including their prices, also increases transparency and accountability of the pharmaceutical industry and of other actors in the supply chain (Kaplan, Wirtz and Laing, 2016^[108]).

Objective:

- Provide accurate updated information about generic medicines available in the market, to inform prescribers, pharmacists and patients on the generic options available and their prices.

Actions:

- Develop a list of medicines (originator and generic/interchangeable medicines) with marketing authorisation that can inform stakeholders on generic substitution options. This list should pool all relevant information of each product.
- Develop a platform, using the aforementioned list, to be used by prescribers and pharmacist to promote generic substitution. This platform should be publicly available. The way in which the information is provided should be previously tested with users to ensure that it is well understood and accessible. The platform should pool and collect real-time information on the prices and availability of medicines in pharmacies and outlets across the country.
- Test effective ways for emphasising generic drugs when structuring the platform – options to be tested could include:
 - **Preselecting the generics option** on prescribing forms.
 - **Adopting bolded, larger fonts** for generics.
 - **Positioning generics and the cheapest options upfront** or presenting options in ascending order by price.

Timeframe:

- The list should be developed starting as soon as possible. The development of the electronic platform should also start as soon as possible and will require the collection of data from several sources, including the prices from pharmacies. The aim of the full development and launch of this platform should be within 3 years.

Institutions/stakeholders involved:

- ISP.
- MINSAL.
- Pharmacies (Pharmacy associations).
- Industry.
- Prescribers (Medical associations).

Policy instrument:

- Pharmaceutical Law 2.
- Regulatory instruments (e.g. reglamento).

Milestones, indicators and evaluation:

- Development and launch of electronic platform with real-time information on medicines available in the Chilean market.
- Use of electronic platform.
- Wide use of electronic platform by the public, prescribers, and pharmacists.
- Increase in the use/sales of generic medicine

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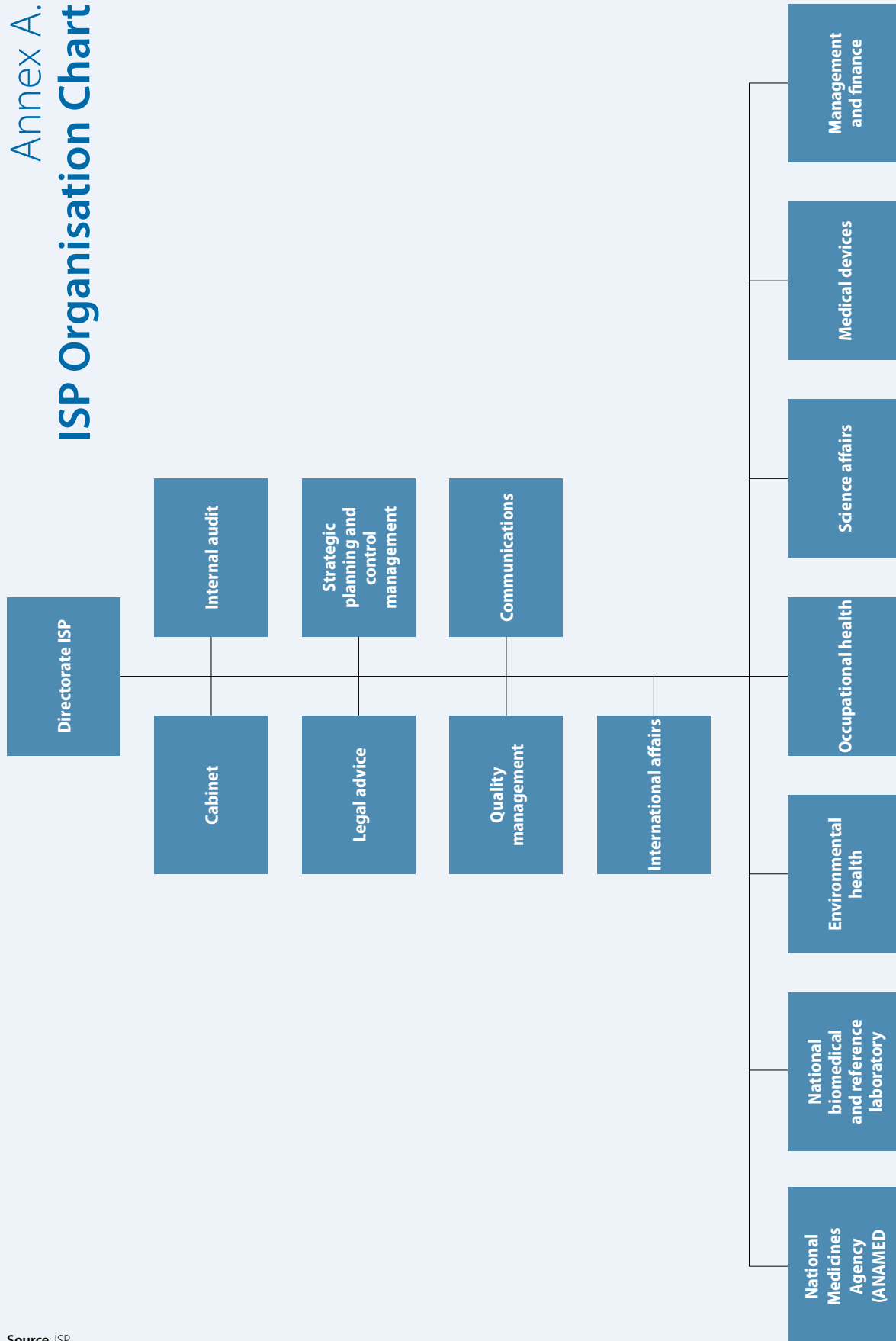
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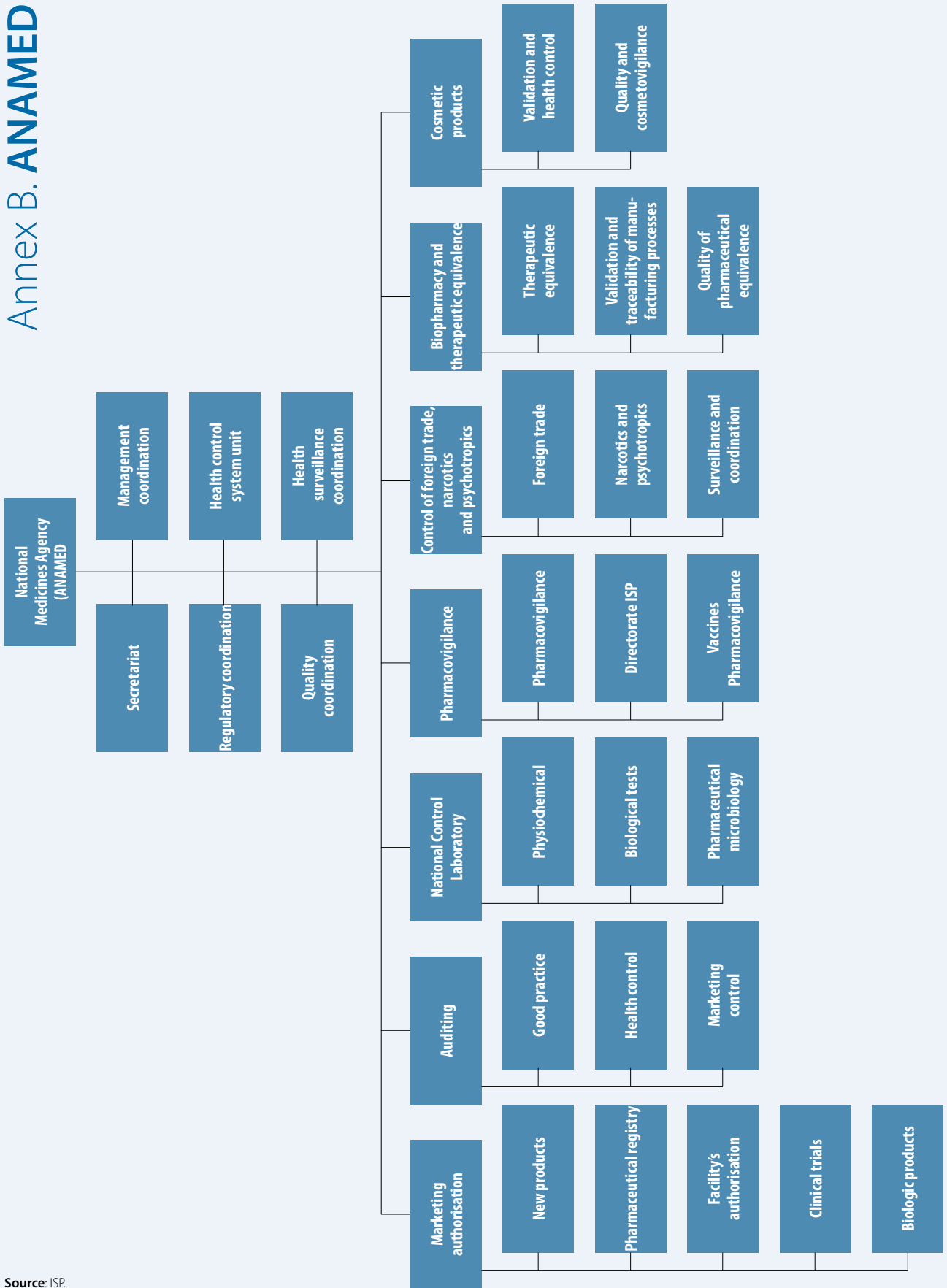
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Annex A. ISP Organisation Chart



Source: ISP.

Annex B. ANAMED



Source: ISP.

Annex C. Glossary

Originator Product (Original Medicine)	The first version of a medicine, developed and patented by an originator pharmaceutical company that has exclusive rights to marketing the product in the European Union for 20 years. An original product has a unique trade name for marketing purposes, the so-called brand name.
Reference Product	A medicine which has been granted a marketing authorisation by a country on the basis of submitted quality, pre-clinical and clinical data, to which the application for marketing authorisation for a generic or a biosimilar product refers.
Generic medicine	<p>A pharmaceutical product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bio-equivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.</p> <p>Generics can be classified in branded generics (generics with a specific trade name) and unbranded generics (which use the international non-proprietary name and the name of the company). The above-mentioned definition refers to European legislation. The World Health Organization (WHO) defines generics as multi-source pharmaceutical products that are therapeutically equivalent, are interchangeable, not taking into consideration of whether or not the 'originator' molecule is, or was, under patent protection.</p>
Pharmaceutical Equivalence	Medicines are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards. Pharmaceutical equivalence does not necessarily imply bio-equivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and absorption.
Therapeutic Equivalent	Two pharmaceutical products are considered therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate bio-equivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.
Bio-equivalence	Two medicinal products are bio-equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.
Interchangeability Interchangeable Medicine	An interchangeable pharmaceutical product is one which is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.
Regulatory Harmonisation	The process by which technical guidelines are developed in order to be uniform across participating authorities in multiple countries.

Regulatory Reliance	The act whereby the MRA in one jurisdiction may take into account and give significant weight to evaluations performed by another MRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others.
Multisource medicine	A medicine that can be purchased under any of several trademarks from different manufacturers or distributors. When the patent of a medicine expires, a single-source medicine becomes multi-source. Multi-source medicines are intended to be pharmaceutically equivalent or pharmaceutical alternatives that are bio-equivalent and hence are therapeutically equivalent and interchangeable. Cf. generic, single-source medicine
Pharmaceutical alternatives	Medicines are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength.

Source: (Kaddu *et al.*, 2018; WHOCC PPRI, 2019)



Annex D.

Regulations Governing Generic Medicines in Chile

Year	Legislation	Descriptions and implications for generic medicines
2004	R No. 515/04	National Policy on Medicines of the Health Reform of the Ministry of Health. Establishes action lines, including: <ul style="list-style-type: none"> – Modifying health regulations related to the quality of medicines to guarantee their equivalence – Establishing conditions for patients to change the originally prescribed medicines for an equivalent generic – Procurement of medicines in the public sector should use INN
2005	R.E. No. 727/05	Approves Norm that defines the criteria destined to establish therapeutic equivalence in pharmaceutical products in Chile.
2008	R.E. No. 4886/08	Technical guidelines for carrying out the bio-equivalence studies of conventional single active ingredient pharmaceutical products and forms for the presentation of the required background for the realisation of said studies. Provides the names and codes of technical guidelines.
2009	R.E. No. 2803/09	Recognises as bio-equivalent products those included in the list of medicines prequalified by the WHO corresponding to products for the treatment of HIV / AIDS, Tuberculosis and Malaria.
2009	R.E. No. 2920/09	Establishes the effective date for the requirement of bio-equivalence studies for pharmaceutical products containing the active ingredients indicated. Establishes a term of one year, starting on July 1, 2009, for the presentation of the bio-equivalence protocol for products containing imatinib mesylate, phenytoin sodium, biperidene hydrochloride, levothyroxine sodium, doxycycline hydrate – hydrochloride, abacavir sulfate, efavirenz, didanosine, fosamprenavir calcic and prednisone.
2009	R.E. No. 5555/09	Modifies Exempt Resolutions No. 728/09 and 2920/09, suspending the requirement of bio-equivalence studies for products containing diclofenac (sodium and potassium) and didanosine.
2009	R.E. No. 5937/09	Establishes reference products for studies of bio-equivalence of immediate-release pharmaceutical products. Similar products containing active ingredients included in this list will be gradually incorporated into the requirement regime for bio-equivalence studies, by establishing the schedules thereof and by publishing the respective resolutions in the Official Gazette.
2011	R.E. No. 244/11	Establishes the effective date for the requirement of bio-equivalence studies for conventional release pharmaceutical products containing the 28 active ingredients indicated in the list. <p>The presentation of the studies to demonstrate therapeutic equivalence will be a requirement for the marketing authorisation of pharmaceutical products that contain the active principles identified above and marketing authorisation will only be granted if the study demonstrates that they are therapeutic equivalents to their respective comparator products, as listed in the present resolution. Companies must submit the corresponding studies within a maximum period of 12 months from February 16, 2011.</p> <p>Similar pharmaceutical products for which no therapeutic equivalence studies are submitted within the deadline will see their marketing authorisation withdrawn.</p>
2011	D.S. No. 3/11	Approves regulations of the national system for the control of pharmaceutical products for human use. Regulations related to pharmaceutical products, including: <ul style="list-style-type: none"> Specifications for marketing authorisation requirements and defines simplified marketing authorisation procedure for pharmaceutical equivalents and therapeutic equivalents Defines pharmaceutical product or medicine Defines therapeutic and pharmaceutical equivalents Defines therapeutic equivalence study and bioavailability study Defines INN Defines reference product Labelling for therapeutic equivalent products
2012	D.E. No. 27/12, Approves Technical Norm No. 131	Approves technical standard No. 131: "Standard that defines the criteria for establishing therapeutic equivalence in pharmaceutical products in Chile". <p>The products that request marketing authorisation and contain one of the active ingredients in the lists approved by the MINSAL must provide studies that prove therapeutic equivalence against the reference product</p>
2012	D.E. No. 448/12, Approves Technical Norm No. 134	Approves the Technical Standard that "Establishes technical specifications of the logo in labels of the containers of those pharmaceutical products that have demonstrated their therapeutic equivalence before the Institute of Public Health (ISP)"

Year	Legislation	Descriptions and implications for generic medicines
2012	D.E. No. 500/12, Approves Technical Norm No. 136	It establishes the regulations that determine the active principles contained in pharmaceutical products that must demonstrate their therapeutic equivalence and list of pharmaceutical products that serve as reference. The Technical Norm 136, in its annex, contains the consolidated lists of active principles of pharmaceutical products that must establish their therapeutic equivalence through in vivo or in vitro studies and the lists of pharmaceutical products that will serve as a reference.
2012	R.E. No. 2274/12	Establishes that the National Agency of Medicines Department will accept as sufficient means to accredit the validation of the productive processes of pharmaceutical products that must demonstrate therapeutic equivalence, the documents certifying compliance with Good Manufacturing Practices issued by any of the following regulatory agencies: European Medicines Agency (EMA); United States Food and Drug Administration; General Directorate of Medicines of the Ministry of Health of Canada; Spanish Agency of Medicines of the Ministry of Health and Consumption; Japanese National Institute of Health Sciences; Agency for the Control of Medicines in the United Kingdom; Swedish Medicines Agency; Agency of Medicinal Products of Switzerland; National Health Surveillance Agency (ANVISA).
2012	D.E. No. 773/12	Modifies D.E. No. 500/12, which approved Technical Norm No. 136. Incorporates reference products into the "List of Reference Products for Therapeutic Equivalence Studies"
2012	D.E. No. 864/12	Modifies D.E. No. 500/12, which approved Technical Norm No. 136. Incorporates reference products into the "List of Reference Products for Therapeutic Equivalence Studies". Provides the term of one year to comply with the requirement of presentation of studies of therapeutic equivalence indicated in the preceding articles.
2012	D.E. No. 904/12	Modifies and clarifies D.E. No. 500/12 that approved Technical Norm No. 136. The period of one month, counted from the publication in the Official Gazette of this decree, is given to holders of sanitary registrations of pharmaceutical products, whose active principles and respective reference products have been alluded to in the third article. The said term shall not apply to pharmaceutical products containing the active ingredients listed in D.E. No. 864/12.
2012	D.E. No. 981/12	Modifies D.E. No. 500/12, which approved Technical Norm No. 136. Incorporates medicines to the "List of Active Principles contained in Pharmaceutical Products that should perform Comparative Studies of In Vivo Bioavailability to demonstrate Therapeutic Equivalence" and incorporates reference products to the "List of Reference Products for Therapeutic Equivalence Studies". It also provides a chronogram and deadlines to comply with therapeutic equivalence studies.
2015	D.E. No. 1157/15	Modifies D.E. 500/12, of the ministry of health, which approves Technical Norm No. 136. Incorporates reference products into the "List of Reference Products for Therapeutic Equivalence Studies"
2013	R.E. No. 1133/13	Application that must be given for the accreditation of validation of productive processes of medicines that must demonstrate bio-equivalence
2013	R.E. No. 1531/13	Scope of the bio-equivalence studies of Pharmaceutical products, which correspond to the same owner and production plant. It is established that in the case of pharmaceutical products of the same owner, of the same formula, including all the excipients, manufactured in the same production plant, with the same raw material, the same origin and whose only difference is solely and exclusively its denomination and registration number, the bio-equivalence studies will be valid for both products
2013	D.E. No. 634/13	Modifies D.E. No. 27/12 that approves Technical Norm No. 131. In the case of pharmaceutical products whose therapeutic equivalence has been certified by National Regulatory Authorities of Regional Reference – Level IV by the Pan American Health Organization, holders of sanitary registration may require the ISP, in a single administrative act, to certify their therapeutic equivalence. In the case of pharmaceutical products included in the list of prequalified medicines of the WHO, they will be recognised as bio-equivalent, for which purpose the holder of the respective sanitary registry must present a document that is certified by the aforementioned organisation.
2013	D.E. No. 858/13	Modification of D.E. No. 27/12 that approves Technical Norm No. 131, and incorporates: ANNEX I called "Bio-equivalence studies to establish Therapeutic Equivalence in solid oral pharmaceutical forms of unconventional release".
2013	D.E. No. 633/13	Modifies D.E. No. 500/12, which approved Technical Norm No. 136. Determines new deadlines to meet the requirement of therapeutic equivalence applicable to listed pharmaceutical products. Determines a list of products to be eligible for the biowaiver of studies "in vivo" to demonstrate their therapeutic equivalence.

Year	Legislation	Descriptions and implications for generic medicines
2013	D.E. No. 1067/13	Modifies D.E. No. 500/12, which approved Technical Norm No. 136. Modifies the period granted by D.E. No. 864/12 regarding the requirement to submit studies of therapeutic equivalence to products containing some of the active principles contained in D.E. No. 500/12. Establishes the schedule for the demonstration of therapeutic equivalence, applicable to listed pharmaceutical products whose products of reference were established in the D.E. No. 864/12. The term of presentation was set by the same administrative act, is as follows: April 30, 2014
2014	D.E. No. 1299/13	Modifies D.E. No. 981/12. Replaces the therapeutic equivalence demonstration period established for pharmaceutical products included in Group C of the same article for December 31, 2015.
2013	R.E. No. 688/13	Determines the list of 100 priority medicines for the execution of plans associated with the national health strategy for compliance with the health objectives of the decade 2011-2020. During this decade, indicators related to the quality of medicines should be improved, considering the fulfilment of norms related to production, storage, distribution, use, therapeutic equivalence, and pharmacovigilance. This list is the focus of several policies towards improving their quality, access, and rational use.
2014	D.E. No. 122/14	Modification D.E. No. 27/12 that approves Technical Norm No. 131. Pharmaceutical products that must demonstrate their therapeutic equivalence through abbreviated studies: aqueous solutions to be administered parenterally; aqueous solutions to be administered orally; medicinal gases; powders to be reconstituted as an aqueous solution; aqueous solutions to be administered by otic or ophthalmic route; aqueous solutions to be administered topically; aqueous solutions to be administered as inhalers or nasal sprays.
2014	D.E. No. 669/14	Modifies D.E. No. 122/14 that modifies the Technical Norm No. 131. Defines deadlines for the demonstration of bio-equivalence through abbreviated studies, granting transitory provisions for sterile and non-sterile pharmaceutical products already registered of a period of six months and one year, respectively, counted from the date of publication of this decree.
2014	Law 20.724 (Pharmaceuticals Law 1)	Modifies the sanitary code regarding the regulation of pharmacies and pharmaceuticals. Includes provisions on: Prescription including INN as optional information Allows generic substitution between medicines that are required to prove therapeutic equivalence only and by patient's request Facilities should have a list of bio-equivalent medicines available for patients Prohibits donations and other type of incentives to prescribers
2014	D.E. No. 123/14	Modifies decree No. 500/12, which approved Technical Norm No. 136. Incorporates pharmaceutical products, and their respective reference products, that need to prove therapeutic equivalence into the "List of active ingredients contained in pharmaceutical products that should perform comparative bioavailability studies in vivo to demonstrate therapeutic equivalence"
2015	D.E. No. 33/15	Modifies D.E. No. 27/12. Modifies deadlines for the demonstration of bio-equivalence through abbreviated studies. Replaces transitory provisions of the D.E. No. 27/12 by the following: transitory provisions: The sterile and non-sterile pharmaceutical products already registered shall comply with the requirements indicated in section 4.2.1 of this standard until December 31 of 2016
2015	D.E. No. 1162/15	Modifies Decrees 981/12 and 123/14 that modified D.E. No. 500/12, which approved Technical Norm No. 136. Incorporates new reference pharmaceutical products. Amends article 4 of D.E. No. 981/12, by replacing the term of December 31, 2015, set for the demonstration of therapeutic equivalence for pharmaceutical products included in Group C, by December 31, 2016.
2016	D.E. No. 644/16	Modifies D.E. No. 500/12 that approved the Technical Norm No. 136. Establishes chronogram to establish therapeutic equivalence and replacing the term of December 31, 2016 set by D.E. No. 1162/15. The chronogram provides deadlines to each listed active ingredients; some product's deadline is established by June 30, 2017, other products by December 31, 2017
2016	D.E. No. 187/16	Modifies D.E. No. 500/12, which approved Technical Norm No. 136. Modifies and incorporates medicines into the "List of Products of Reference for the Studies of Therapeutic Equivalence". Modifies and incorporates products to the reference products list
2016	D.E. No. 257/16	Modifies the D.E. No 27 that approved the Technical norm No. 131, and D.E. No. 500 that approved the Technical Norm No. 136. Allows a period of two years, counted from the publication in the Official Gazette of this decree, so that holders of pharmaceutical products that meet the characteristics indicated in this decree can submit to the ISP the studies to demonstrate bio-equivalence.
2016	D.E. No. 544/16	Modifies the D.E. No. 27/12. Modifies Annex 1 regarding bio-equivalence studies on oral non-conventional solid pharmaceutical forms of the Technical Norm No. 131. Modification relates to capsules with micro granules.

Year	Legislation	Descriptions and implications for generic medicines
2018	D.E. No. 115/18	Modifies D.E. No. 500/12, which approves Technical Norm No. 136. Merges the lists “List of Reference Products for Therapeutic Equivalence Studies” and “List of Reference Products for the Therapeutic Equivalence Studies of Modified Release Medicines” into a single one that will be called “List of Reference Products for The Studies of Therapeutic Equivalence”, and incorporates more reference products/medicines into the list. Establishes timelines for each medicine to provide therapeutic equivalence (18 months to 3 years after the publication of this decree)
2018	D.E. No. 112/18	Modifies D.E. No. 27/12 and D.E. No. 500/12. Pharmaceutical products that containing at least one active ingredient, have any of the characteristics indicated, must demonstrate their therapeutic equivalence: aqueous solutions to be administered parenterally, aqueous solutions to be administered orally, powder to be reconstituted as an aqueous solution, medicinal gases, aqueous solutions to be administered via otic or ophthalmic, aqueous solutions to be administered topically, and aqueous solutions for nebulisation or spray. Allows time until October 1, 2020, so that holders of health records of pharmaceutical products that meet some of the characteristics indicated above submit to the ISP the background to demonstrate bio-equivalence.
2018	D.E. No. 127/18	Suspends requirement of demonstration of therapeutic equivalence, contained in D.E. No. 500/12, which approved Technical Norm No. 136. Suspends the requirement of demonstration of therapeutic equivalence of pharmaceutical products containing the active principles indicated in this decree.

Note: R – Resolution; R.E. – Exempt Resolution (Resolución Exenta); D.S. – Supreme Decree (Decreto Supremo); D.E. – Exempt Decree (Decreto Exento); INN – International Non-proprietary Name; WHO – World Health Organization; ISP – Institute of Public Health (Instituto de Salud Pública); MINSAL – Ministry of Health (Ministerio de Salud); CENABAST – Central Supply of the National System of Health Services (Central de Abastecimiento del Sistema Nacional de Servicios de Salud)

Source: ISP (Instituto de Salud Pública, no date)



Annex E. Pharmaceutical equivalence studies to establish interchangeability of medicines and for marketing authorisation

	Chile (ISP)	Mexico (COFEPRIS)	Brazil (ANVISA)	United States (FDA)	European Union (EMA)	Australia (TGA)
Bio-equivalence (BEQ) Studies (in vivo studies)	Comparative bioavailability studies	Interchangeability tests: Comparative bioavailability studies Specific tests for Inhalers	Comparative bioavailability studies	Comparative bioavailability studies	Comparative bioavailability studies	Comparative bioavailability studies
Which medicines?	Oral solid products of immediate release Products of narrow therapeutic margin (NTM); modified release and systematically distributed Formulated in fixed associations, conventional release, systematically absorbed and distribute	All oral pharmaceutical forms of immediate release of systemic action All non-oral pharmaceutical forms of systemic action Suspensions and emulsions Medications for inhaled administration Medicines with NTM	All oral pharmaceutical forms of immediate release of systemic action All non-oral pharmaceutical forms of systemic action Medicines with NTM	All oral pharmaceutical forms of immediate release of systemic action All non-oral pharmaceutical forms of systemic action Medicines with NTM	Oral pharmaceutical forms with immediate release formulations with systemic action.	Oral tablets and capsules, oral suspensions, complex intravenous solutions for injection, medicines – applied locally (e.g., inhalational and nasal medicines, ocular, dermal, rectal or vaginal administration) where the drug substance is acting systemically, transdermal medicines.
Guidelines for conduct of studies	Yes	Yes	Yes	Yes	Yes	Yes
Number of participants	Calculated with appropriate methods. Min 12, usually 18-24 subjects.	Calculated with appropriate methods. Min 12.	Based on appropriate sample size calculation.	At least 12 subjects	Based on appropriate sample size calculation. Min 12 subjects	Based on appropriate sample size calculation. Min 12 subjects
Pharmacokinetic parameters	ABC, Cmax, tmax, dissolution profile, others.	ABC0-t, ABC0-∞, Cmax, tmax, Ke and t1/2	ABC0-t, ABC0-∞, Cmax, tmax, Ke and t1/2	Rate of absorption, the extent of absorption, the half-life of the therapeutic moiety in vivo, and the rate of excretion and/or metabolism. Single-dose BEQ studies: AUC0-t, AUC0-∞, Cmax, Tmax, Kel and t1/2 Steady dose BEQ studies: AUC0-tau, CmaxSS, CavSS, degree of fluctuation [(Cmax-Cmin)/(CavSS)], swing [(CmaxSS-CminSS)/CminSS], and Tmax.	Single dose, AUC(0-t), AUC(0-∞), residual area, Cmax and tmax should be determined. In studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, AUC(0-∞) and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, AUC(0-72h), λz, and t1/2. For immediate release formulations at steady state, AUC(0-t), Cmax,ss, and tmax,ss should be determined. When using urinary data, Ae(0-t) and, if applicable, Rmax.	Single dose, AUC(0-t), AUC(0-∞), residual area, Cmax and tmax should be determined. In studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, AUC(0-∞) and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, AUC(0-72h), λz, and t1/2. For immediate release formulations at steady state, AUC(0-t), Cmax,ss, and tmax,ss should be determined. When using urinary data, Ae(0-t) and, if applicable, Rmax.

	Chile (ISP)	Mexico (COFEPRIS)	Brazil (ANVISA)	United States (FDA)	European Union (EMA)	Australia (TGA)
Acceptability Criteria	CI 90% BEQ acceptance interval 80 – 125% for AUC and Cmax For medicines with NTM: BEQ acceptance interval 90-111.11% for AUC and Cmax	CI 90% BEQ acceptance interval 80 – 125% for AUC and Cmax For medicines with NTM: BEQ acceptance interval 90-111.11% for AUC and Cmax	CI 90% BEQ acceptance interval 80 – 125% for AUC and Cmax For medicines with NTM: BEQ acceptance interval 90-111.11% for AUC and Cmax	CI 90% BEQ acceptance interval 80 – 125% for AUC and Cmax For medicines with NTM: BEQ acceptance interval 90-111.11% for AUC and Cmax	CI 90% BEQ acceptance interval 80 – 125% for AUC and Cmax For medicines with NTM: BEQ acceptance interval 90-111.11% for AUC and Cmax For highly variable drug products (HVPD): BEQ acceptance interval 69.84-143-19% for Cmax	CI 90% BEQ acceptance interval 80 – 125% for AUC and Cmax For medicines with NTM: BEQ acceptance interval 90-111.11% for ABC and Cmax For highly variable drug products: BEQ acceptance interval 69.84-143-19% for Cmax
Biowaivers (in vitro studies)	Dissolution profile	Dissolution profile	Dissolution profile	Dissolution profile	Dissolution profile	Dissolution profile
Which medicines?	Oral solid forms of immediate release and highly soluble Product in a different strength and similar in its active and inactive ingredients to another drug product for which BEQ has been tested	Oral solid forms of immediate release and highly soluble. Product in a different strength and similar in its active and inactive ingredients to another drug product for which BEQ has been tested	Immediate-release generic medication and modified-release solid forms (delayed or prolonged), in various strengths.	Product in a different strength and similar in its active and inactive ingredients to another drug product for which BEQ has been tested	Product in a different strength and similar in its active and inactive ingredients to another drug product for which BEQ has been tested Highly soluble substances Based on Biopharmaceutical Classification System-based biowaiver approach	Based on Biopharmaceutical Classification System-based biowaiver approach
Guidelines for conduct of studies	Yes	Yes	Yes	Yes	Yes	Yes
Measures/parameters	Similarity factor (f2)	Similarity factor (f2)	Similarity factor (f2)	Similarity factor (f2)	Similarity factor (f2)	Similarity factor (f2)
Acceptability criteria	≥85% of the AI dissolves in 30min in 90mL in three buffers (pH 1.2, 4.5, and 6.8) And f2 ≥ 50 Variation coefficient ≤20% Or ≥85% solubility in ≤15min in the three buffers	≥85% of the AI dissolves in 30min in 90mL in three buffers (pH 1.2, 4.5, and 6.8) And f2 ≥ 50 Variation coefficient ≤20% Or ≥85% solubility in ≤15min in the three buffers	≥85% of the AI dissolves in 30min in 90mL in three buffers (pH 1.2, 4.5, and 6.8) And f2 ≥ 50 Variation coefficient ≤20% Or ≥85% solubility in ≤15min in the three buffers	≥85% of the AI dissolves in 30min in 90mL in three buffers (pH 1.2, 4.5, and 6.8) And f2 ≥ 50 Variation coefficient ≤20% Or ≥85% solubility in ≤15min in the three buffers	≥85% of the AI dissolves in 30min in 90mL in three buffers (pH 1.2, 4.5, and 6.8) And f2 ≥ 50 Variation coefficient ≤20% Or ≥85% solubility in ≤15min in the three buffers	≥85% of the AI dissolves in 30min in 90mL in three buffers (pH 1.2, 4.5, and 6.8) And f2 ≥ 50 Variation coefficient ≤20% Or ≥85% solubility in ≤15min in the three buffers
Other quality specifications for marketing authorisation	Do not require BEQ studies, BEQ is self-evident	Do not require BEQ studies, BEQ is self-evident	Results of pharmacodynamic studies that support therapeutic equivalence should be presented	Do not require BEQ studies, BEQ is self-evident	Where bio-equivalence cannot be demonstrated, requires that the results of appropriate pre-clinical tests or clinical trials will be provided.	Do not require BEQ studies, BEQ is self-evident

	Chile (ISP)	Mexico (COFEPRIS)	Brazil (ANVISA)	United States (FDA)	European Union (EMA)	Australia (TGA)
Which medicines?	Aqueous solutions (parenteral use, oral use, ophthalmic, otic or topical use) Gases Powder for aqueous solutions Inhalers	Aqueous solutions (parenteral use, oral use, ophthalmic, otic or topical use) Gases Products for ophthalmic, otic, nasal, oral, topical, rectal and vaginal with non-systemic use	Intravenous, intramuscular, subcutaneous or intrathecal aqueous solutions Oral solutions Reconstitution powders Gases Aqueous otic and ophthalmic solutions Topical non-systemic medicinal products Inhalation medicinal products or nasal sprays	Parenteral solution for injection; ophthalmic or otic solution. Inhaling gas Solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolisation or nebulisation, a nasal solution, or similar other solubilised form	Aqueous intravenous solution Gas for inhalation Solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolisation or nebulisation, a nasal solution, or similar other solubilised form	Medicinal gases, peritoneal dialysis solutions, simple aqueous solutions for intravenous injection or infusion, oral solutions, medicines containing drug substances that are not systemically or locally absorbed, medicines applied locally
Applicable Regulation	D.S. 3 (Ref) Norma Técnica N° 131	NOM-177-SSA1-2013 Agreement that determines the type of test to demonstrate interchangeability	Resolução da Diretoria Colegiada – RDC n 200 de 26-12-2017 Consolidado de normas de bio-equivalencia	21 CFR 320 21 CFR 314	Guideline on the investigation of bio-equivalence for EMA (CPMP/EWP/QWP/1401/89)	Therapeutic Goods Act 1989 (The Act) Guideline on the investigation of bio-equivalence for EMA (CPMP/EWP/QWP/1401/89)

Note: BEQ – bio-equivalence; AI – active ingredient; CI – Confidence Interval; NTM – Narrow Therapeutic Margin; NRA – National Regulatory Agency; ISP – Instituto de Salud Pública (Institute of Public Health); COFEPRIS – Comisión Federal para la Protección contra Riesgos Sanitarios (Federal Commission for Protection against Health Risks); ANVISA – Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency); FDA – Food and Drug Administration; EMA – European Medicines Agency; TGA – Therapeutic Goods Administration).

Pharmacokinetic parameters: AUC – Area Under the Curve // C_{max} – peak plasma concentration // t_{max} – time to reach C_{max} // t_{1/2} – elimination half-time // K_{el} – elimination rate constant // λ_z – terminal elimination rate constant // R_{max} – maximum response

Source: Based on each country's applicable regulations



Over the last few decades, Chile has achieved significant improvements in key health indicators: from increased life expectancy across the country to high growth in health expenditure and improved standards for the approval of generic medicines in line with international practice. Despite the significant improvements, persisting challenges impact the Chilean health system. Critically, out-of-pocket spending for health as share of final household's consumption is the highest in the OECD. Moreover, limited capacity and resources accentuate inefficiencies in marketing approval procedures for new medicines, creating backlogs and long waiting times. Challenges also strain the market of generic drugs, where obstacles to competition persist; confusion on the definition and quality of bioequivalent products hinders higher uptake of generic drugs; and many producers are failing to comply with the latest bioequivalence criteria.

At the request of the Government of Chile, the OECD conducted a detailed Assessment that lays out a number of suggested policy actions based on international practices to further improve the ongoing efforts to ensure an efficient and well-functioning pharmaceutical sector, while enhancing the productivity and competitiveness of the economy. To help address the cross-sectoral nature of the issues at stake, the Assessment was prepared by an OECD multidisciplinary team with experts from the Economics Department, the Employment, Labour and Social Affairs Directorate and the Directorate for Financial and Enterprise Affairs. The OECD team worked closely with a number of Chilean institutions, including with key government institutions, private sector, research institutions and civil society.

